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THE REVERSE ANOMERIC EFFECT

by



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The undersigned certify that they have read, and recommend to
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ABSTRACT

The main purpose of this research was to prepare the *N*-D-glucopyranosyl, *N*-D-mannopyranosyl and *N*-D-ribofuranosyl imidazoles and to examine their conformational equilibria in solution. The existence of the reverse anomeric effect was established by a comparative study of the conformational behavior, in solution, of these compounds with those of their *N*-protonated and *N*-methylated derivatives, employing proton magnetic resonance spectroscopy.

The required anomers, of hexopyranosyl imidazoles of the D-*gluco* and D-*manno* configurations, and of D-ribofuranosyl imidazole, were obtained in pure state by reaction of the corresponding glycosyl bromides with imidazole followed by the isolation of the products by column chromatography. "Orthoamide" type compounds, for example tri-*O*-acetyl-1',2'-*O*-(1-*exo-N*-imidazolyl ethylidene)- α -D-glucopyranose were found to be the first products of the reaction of a glycosyl bromide with imidazole and these were subsequently converted to *N*-glycosides. The mechanism of formation of *N*-glycosyl imidazoles is discussed.

As expected, the β -*N*-*gluco* and the β -*N*-mannopyranosyl imidazoles, which carry the imidazole ring in equatorial orientation, did not undergo appreciable change from the 4C_1 conformation on either *N*-protonation or *N*-methylation, of the imidazole ring. However, *N*-tetra-*O*-acetyl- α -D-*gluco* and α -D-mannopyranosyl imidazoles exhibited, on *N*-protonation and *N*-methylation, a ${}^4C_1 \rightleftharpoons {}^1C_4$ conformational equilibrium in which 1C_4 conformation has the aglycon in the equatorial orientation (the reverse anomeric effect). This equilibrium depended

on the strength and the concentration of the acid used for protonation. On the other hand, the β -*N*-ribofuranosyl imidazoles existed in C_2' -*endo* $\rightleftharpoons$ C_3' -*endo* conformational equilibrium and on *N*-methylation of the imidazole ring the population of the C_3' -*endo* conformation was increased. An attempt has been made to explain the conformational behavior of some purine and pyrimidine nucleosides and nucleotides in the light of the above findings. α -*N*-Ribofuranosyl imidazoles did not show such conformational changes.

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<u>61</u>	7-Methyl guanosine	146
<u>62</u>	1,7-Dimethyl guanosinium iodide	146
<u>63</u>	3-Methyl-1-(tri- <i>O</i> -acetyl- α - <u>D</u> -ribofuranosyl)-imidazolium iodide	-

<u>64</u>	1-(α -D-Ribofuranosyl)-imidazole	-
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I INTRODUCTION

A. The Anomeric Effect

It has long been known that for derivatives of $\underline{\underline{D}}$ -glucopyranose, the α -configuration at the anomeric center is thermodynamically more favorable than the β -configuration (see ref. 1 for review). As information on the configuration of the anomeric center of sugars and glycopyranosides accumulated (2-7), it became evident that electro-negative glycosyl substituents such as halogens, alkoxy, and acyloxy prefer the axial orientation to the equatorial one. The free energy difference between an axial and equatorial acetoxy group on a cyclohexane ring is 0.66 kcal/mole in favor of the latter at 25°C in carbon disulfide (8) or carbon tetrachloride (9). This so-called A value (10), for the methoxy group is 0.6 kcal/mole, also in favor of the equatorial position (9). On the other hand, the free energy difference between penta-*O*-acetyl- α - $\underline{\underline{D}}$ -glucopyranose and penta-*O*-acetyl- β - $\underline{\underline{D}}$ -glucopyranose is 1.1 kcal/mole at 25°C in a mixture of acetic anhydride and acetic acid in favor of the α -anomer (11,12). This preference of the anomeric acetoxy, halogeno, and methoxy substituent in pyranoside structures for the axial position is fairly general. This phenomena was termed the "Anomeric Effect" by Lemieux and Chü (13) and is the subject of this review.

Lemieux and Brice (14) have shown that tetra-*O*-acetyl- β - $\underline{\underline{D}}$ -glucopyranosyl chloride is converted in the presence of titanium tetrachloride to the more stable α -anomer in 90% yield. Lemieux and Shyluk (15) have reported yields of over 90% of the α -anomer when methyl-tetra-*O*-acetyl- β - $\underline{\underline{D}}$ -glucopyranoside is anomerized using boron trifluoride or

titanium tetrachloride as a catalyst. Indeed, some difficultly available α -glycosides have been prepared by anomerization of the corresponding β -anomers (16).

Sugar acetates undergo similar anomerization. A quantitative study of the anomerization equilibria for the per-*O*-acetyl derivatives of sugars was carried out by Lemieux and Chü (13,17). These authors based their calculations on two assumptions: (i) the geometry of the pyranose ring is similar to that of the cyclohexane ring and (ii) the free energy difference between a set of conformational isomers is that arising from differences in non-bonded interactions which can be considered as addition function. It should be noted, however, that these assumptions are approximations. The X-ray crystal structure analyses of a number of sugar pyranoses indicate that the valence angle at the ring oxygen atom is mostly greater than that at the carbon atoms, which seem to counteract the effect of the two short carbon oxygen bonds (C_5-O_5 and C_1-O_5), when compared with carbon-carbon bonds of cyclohexane (3,4). From this, it may be inferred that distances between the ring carbon atoms of the pyranose ring are not very different from those in the regular cyclohexane ring, unlike those of the 1,3-dioxane system in which four of the bonds are shorter and some of the axial-axial distances may be much less than in cyclohexane (18). The calculation of the various non-bonded interaction energies for pentopyranose tetraacetates were carried out and the following values for the interaction free energies in kcal/mole were obtained (13,17). One oblique stroke is used to indicate the non-bonded interaction between two atoms in *gauche* relationship and two oblique strokes to indicate *syn*-diaxial interaction. A is the value of the anomeric effect.

$$O//H - H//H = 0.17$$

$$O/O - H/H = 0.54$$

$$O//O - H//H = 2.05$$

$$A = \text{Anomeric Effect} = 1.27$$

The anomeric effect for the hexose pentaacetates was calculated to be of the order of 1.42 kcal/mole. Using this value for the anomeric effect and the other values mentioned above for the changes in non-bonded interactions, the anomerization equilibria expected for the hexose acetates were calculated as shown in Table 1.

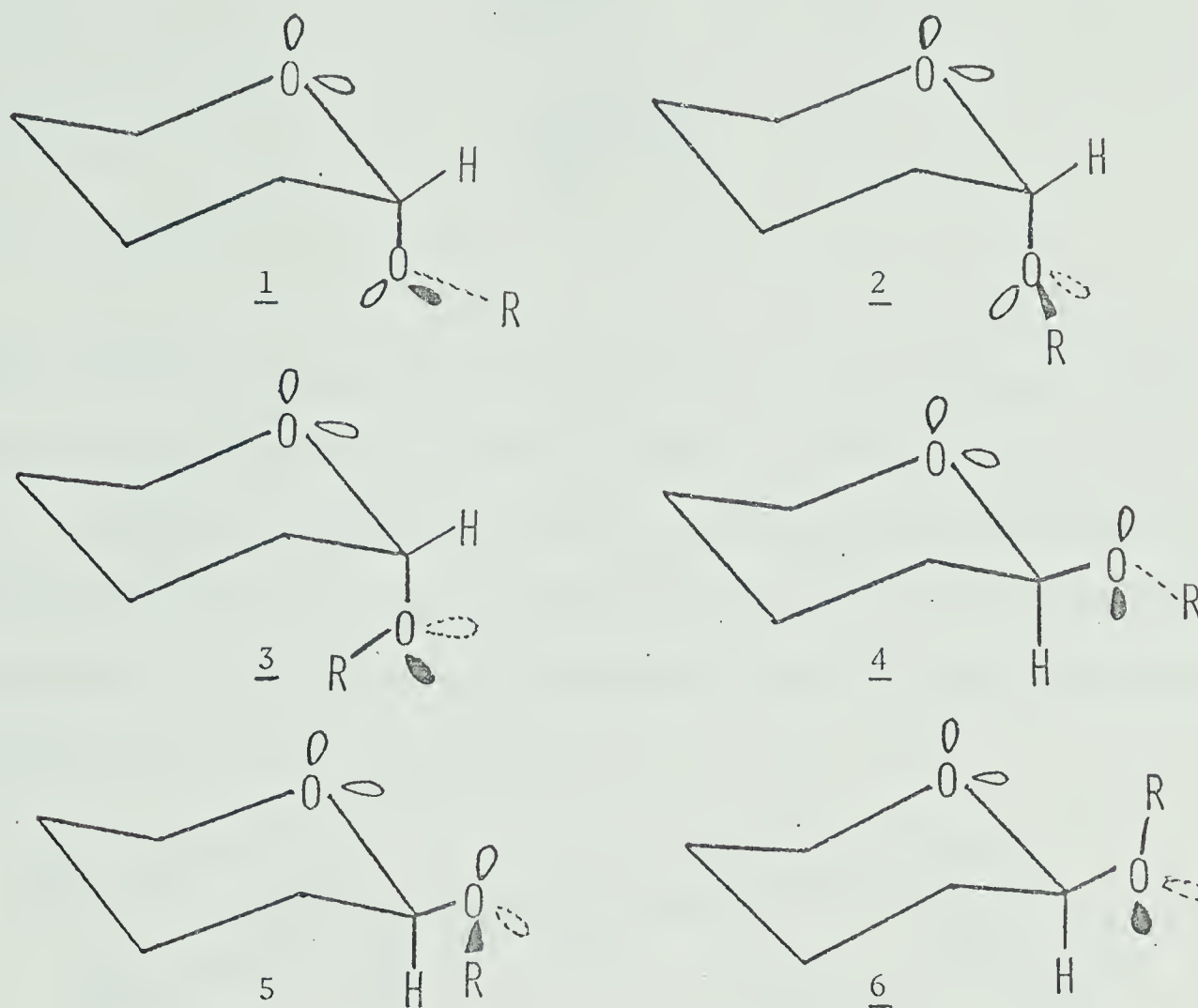
TABLE 1

Anomerization equilibria for hexopyranose pentaacetates

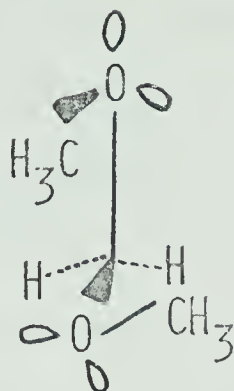
Configuration	Analysis	ΔF° , kcal/mole	
		Found	Calculated
Gluko	1.42 - 0.33	1.10	1.09
Manno	1.42 + 0.54 - 0.33	1.69	1.63
Allo	1.42 - 2.05	-0.45	-0.63
Galacto	1.42 - 0.33	1.15	1.09
Altro	1.42 + 0.54 - 2.05	-0.31	-0.09
Talo	1.42 + 0.54 - 0.33	1.62	1.63
Gulo	1.42 - 2.05	-0.45	-0.45

It is apparent from the above table that there is good agreement between the found and the calculated values. In this way, the existence of the anomeric effect was first firmly established through a study of compounds of known conformations.

For each anomer of a glycoside, at least three rotational isomers are possible (17,19,20),

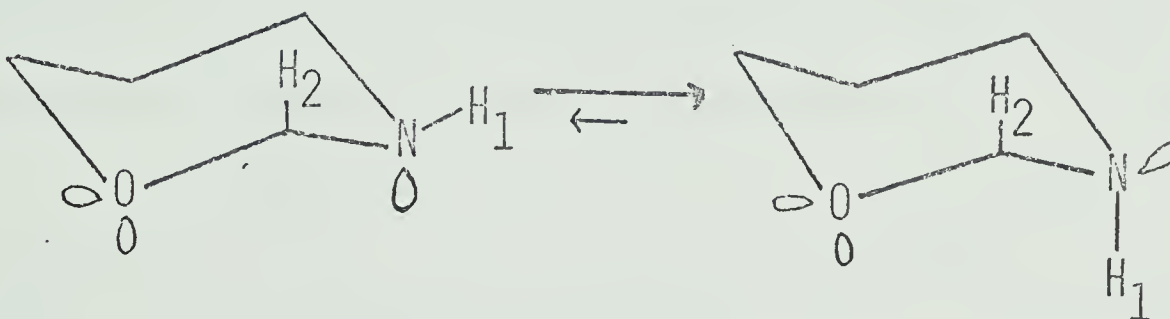


whereas in the case of an axial aglycon (OR), 1 is the only conformation in which no e//e interaction is present; in the case of an equatorial anomer either one or two e//e interactions are invariably present. The most stable conformation with an equatorial aglycon is 4. So the tendency for the R group of both α - and β -anomers is to be antiparallel to C₁-C₂ bond and this has recently been termed the *exo* anomeric effect by Lemieux, Pavia *et al.* (21). Thus, it is apparent now why the aglycon OR prefers the axial orientation to the equatorial one. It was not surprising (17), therefore, that the dipole moment measurements indicated that dimethoxy methane exists in the *gauche-gauche* conformation as shown below (22):

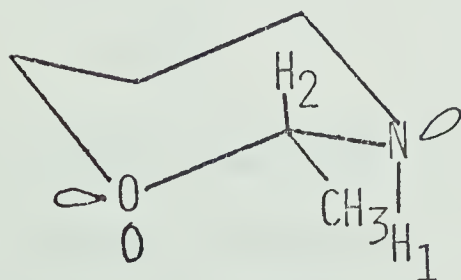


This structure has since been substantiated through electron diffraction (23) and nuclear magnetic resonance studies of O^{17} -dimethoxy methane (24).

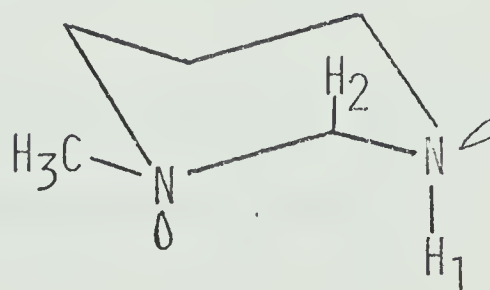
Recently, Lemieux and Booth (25) concluded from the magnitude of the coupling constants between N-hydrogen and the vicinal axial hydrogens of perhydro 1,3-oxazine and 1,3-diazine, that the stable conformation has the N-H in axial orientation.



$$J_{1,2} = 13.1 \text{ Hz } (-80^\circ)$$



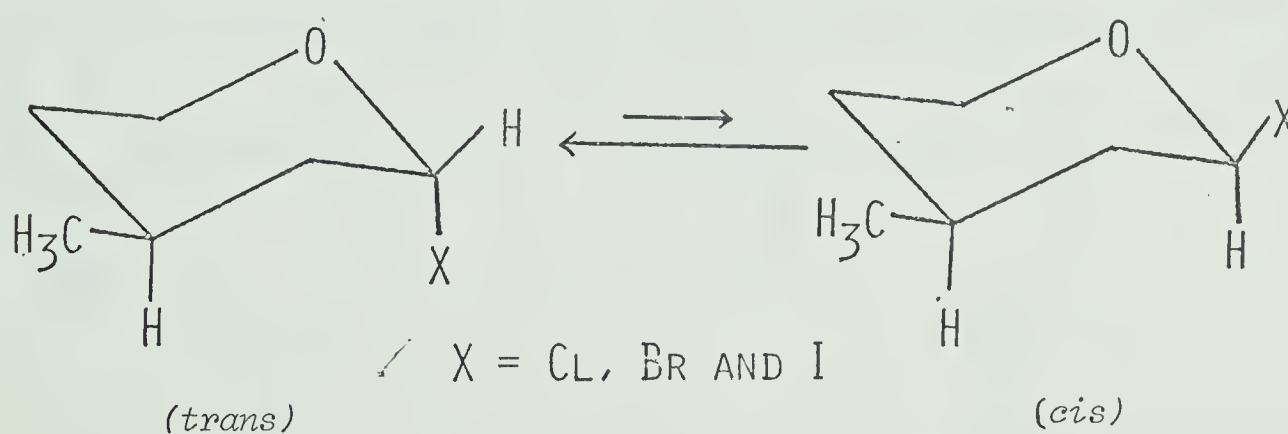
$$J_{1,2} = 12.6 \text{ Hz } (-50^\circ\text{C})$$



$$J_{1,2} = 13.0 \text{ Hz } (-70^\circ)$$

Eliel (26) has also reported similar observations and has termed the e//e interaction "the rabbit-ear effect." Since the anomeric center is found, by definition, only in glycosyl structures but the phenomena concerned with the anomeric effect is not restricted to such structures alone, but also found in non-carbohydrate structures; the term, "generalized anomeric effect" was introduced recently (27).

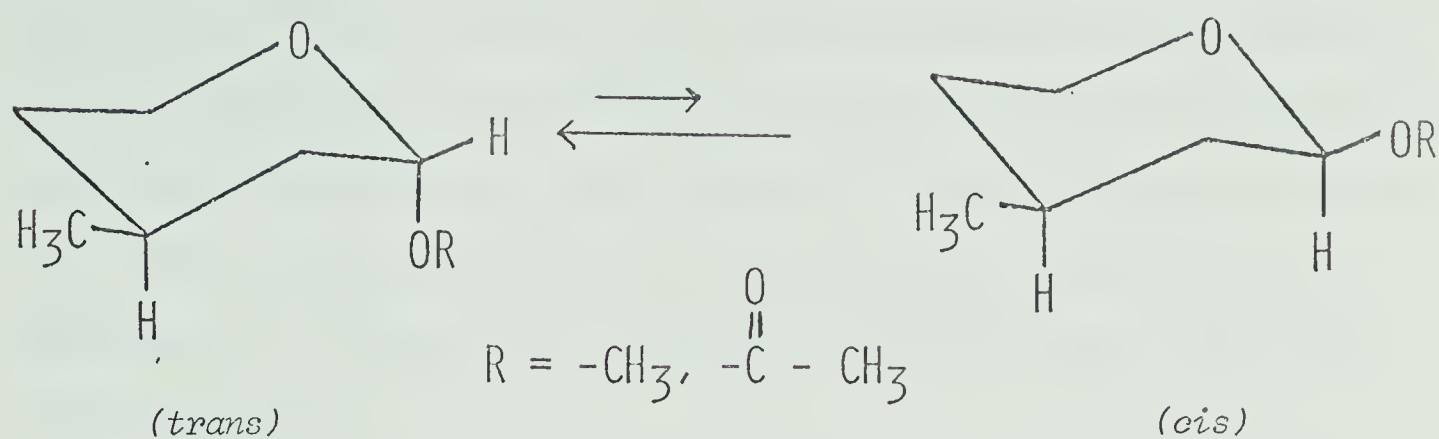
The generalized anomeric effect is also observed with the derivatives of tetrahydropyran. Lemieux and Fraser-Reid (28) have reported that *trans*-2,3-dichlorotetrahydropyran exists entirely in that conformation in which both the chlorine atoms are in axial orientation. Booth and Ouellette (29) observed, through nuclear magnetic resonance (n.m.r.) spectroscopy, that 2-chloro- and 2-bromo-tetrahydropyrans existed mainly in that conformation which had the halogen substituent in the axial orientation. Anderson and Sepp (30) studied the conformational equilibria of 2-halo-4-methyl-tetrahydropyrans by a similar method.



Their results showed that at equilibrium 97% or more of the *trans*-2-halo-4-methyl tetrahydropyran, which had the halogen atom in the axial orientation was present.

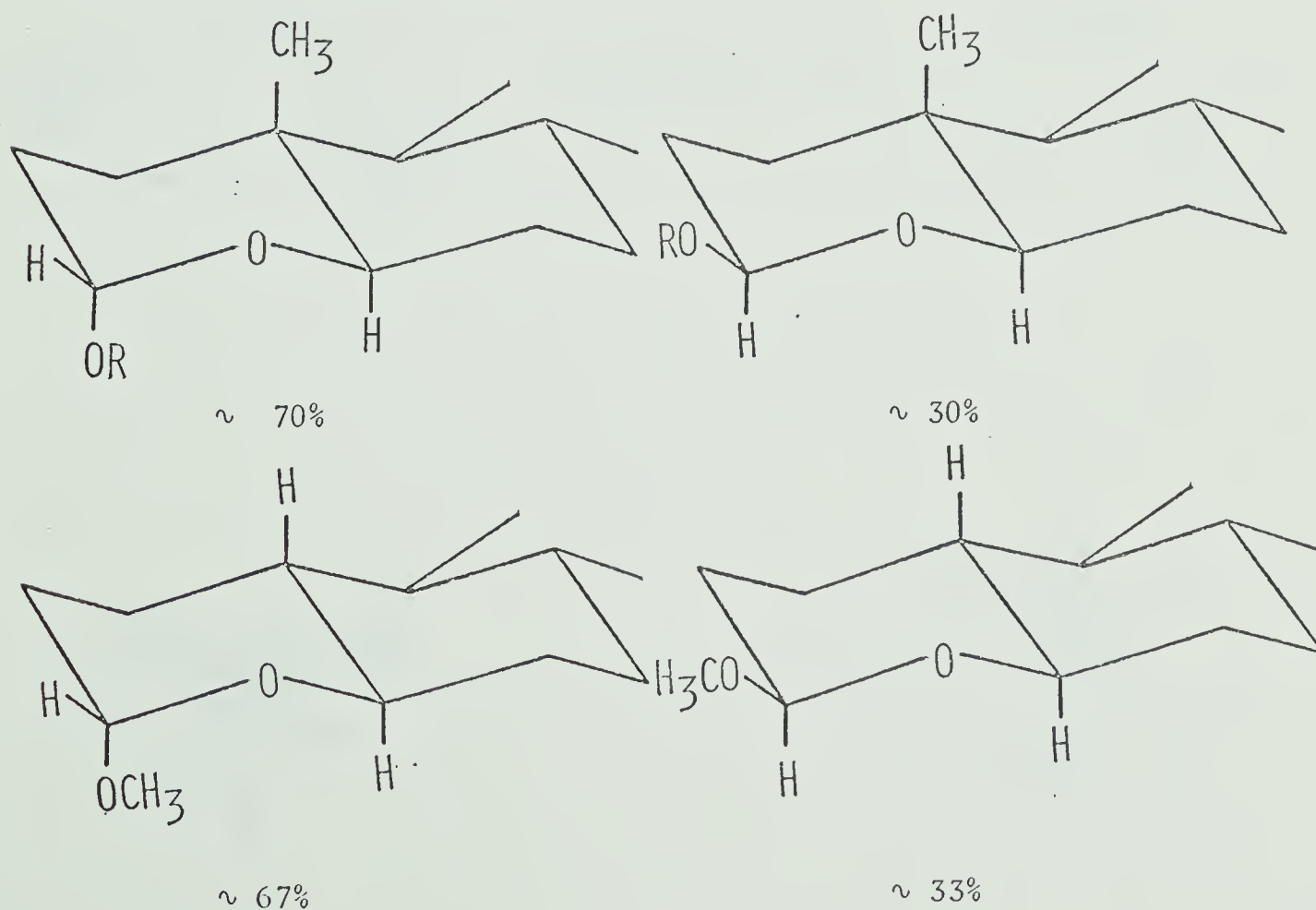
In the case of 2-acetoxy- and 2-methoxy-4-methyl-tetrahydropyrans, the *trans*-diaxial forms are more stable as compared to the *cis*-equatorial

isomers (20,31-36). The equilibrium mixtures contained 65% of the



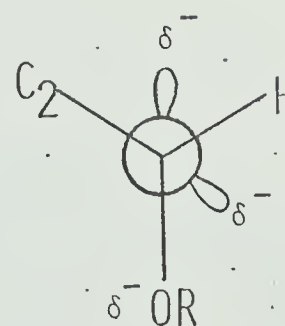
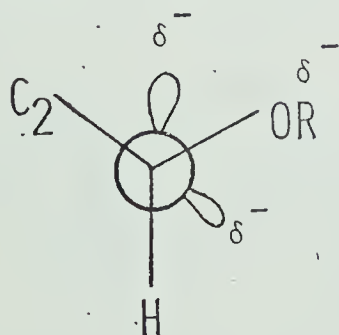
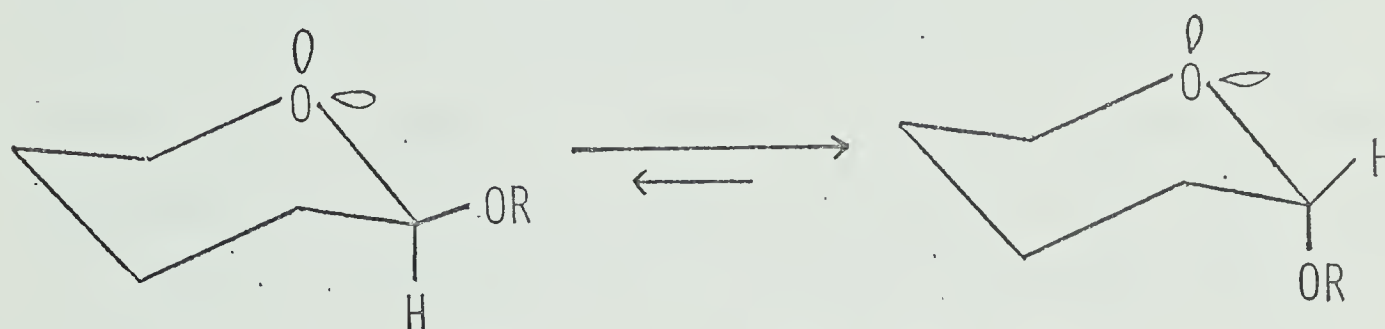
trans-2-methoxy- and 70-75% of the *trans*-2-acetoxy-4-methyl tetrahydropyrans.

Edward and coworkers also observed the generalized anomeric effect in steroids. The axial α -forms of 3-alkoxy-4-oxa-5- α -cholestanes (37,38) and 3-methoxy-4-oxa-5- α -estrans (39) predominate over their

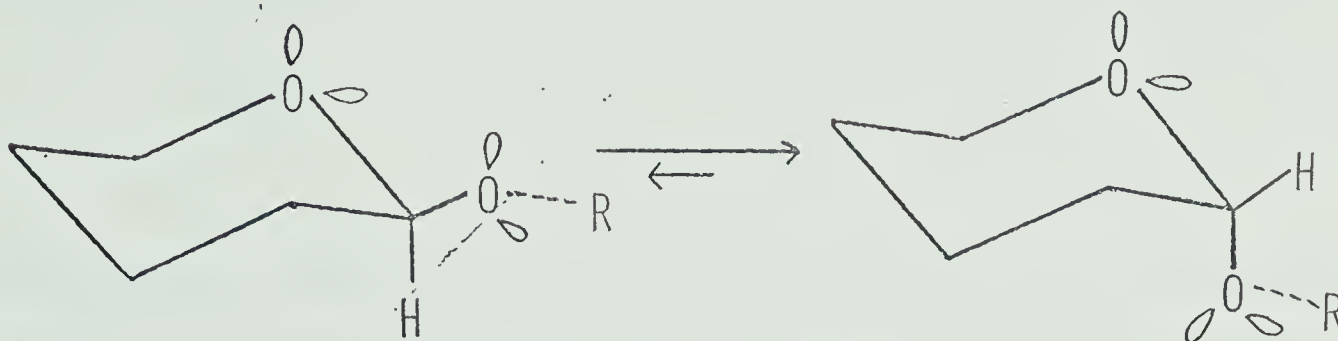


β -equatorial anomers at equilibrium. Katritzky and coworkers (40) reported in 1965 that 2-methoxy and 2-ethoxy-carbonyl-1,4-benzodioxane exist to the extent of about 70% in a conformation with the substituent in the axial orientation. X-ray analysis and dipole moment measurements have shown that halogenodioxanes and dithianes also showed a strong preference for conformations which had the halogen atoms in the axial orientation (41-51).

Several theories have been put forward to explain the origin of the anomeric effect (13,17,52,53). Edward (52) in 1955 proposed that in the equatorial orientation at the anomeric center there exists severe repulsion between the polar C-O bond and the para orbitals of the ring oxygen. This is illustrated below by means of Newman projections across the C₁-O bond of the α - and β - anomers.

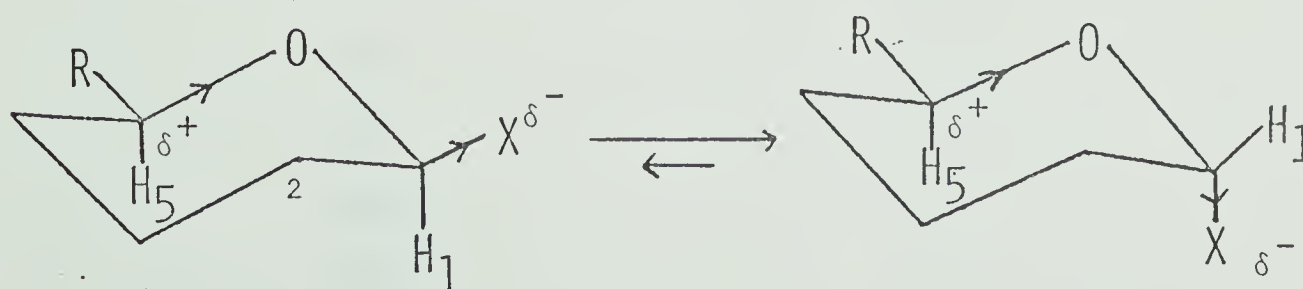


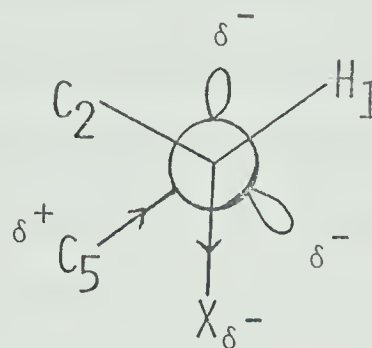
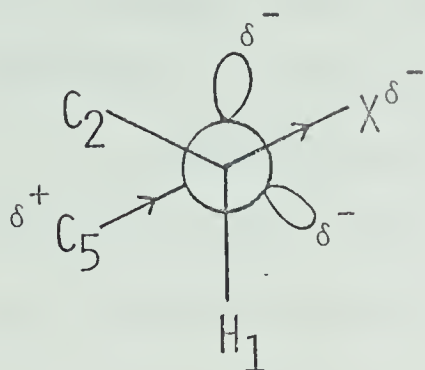
Kabayama and Patterson (53) have also attributed the anomeric effect to the repulsion between the lone pair electrons of the ring oxygen atom and the C₁-oxygen atom. They explained that on going from the equatorial



anomer to the axial anomer, the *syn*-diaxial interactions arising from the orbitals of the unshared pairs of electrons are released. As mentioned earlier, Eliel (26) has termed the e//e interaction the "rabbit ear effect," assuming this to be the main origin for the anomeric effect. However, it must be kept clearly in mind that the existence of the "rabbit ears" as p-orbitals is strictly an intuitive hypothesis based on qualitative molecular orbital theory. To date, the only evidence based in *ab initio* quantum mechanical calculations (54) predicts the rabbit ear effect to be an example of the "Harvey" phenomena (55).

Lemieux and Chü (13,17) suggested that in the axial orientation of the aglycon the dipoles of the C₁-X bond and the C₅-O₅ bond are more favorably oriented as illustrated below:

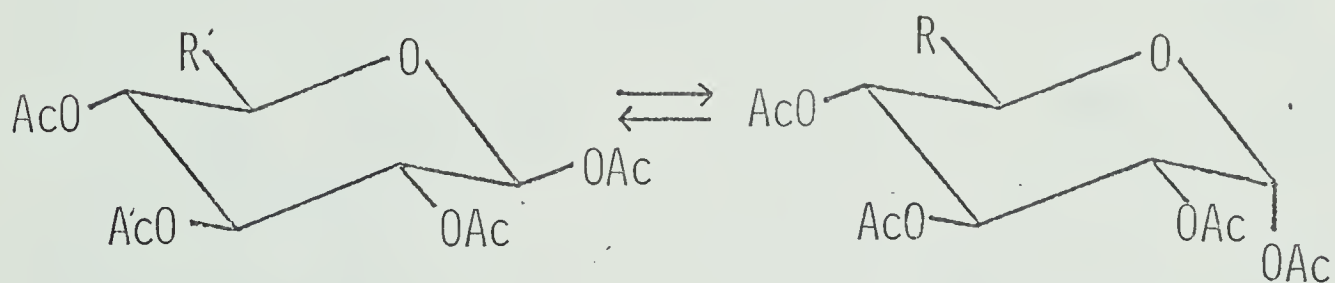




Experimental evidence in support of this hypothesis was obtained from a study of the effect of varying the equatorial C₅-substituent of the tetra-*O*-acetyl-D-xylopyranoses on the magnitude of the anomeric effect and the data are reproduced in Table 2.

TABLE 2

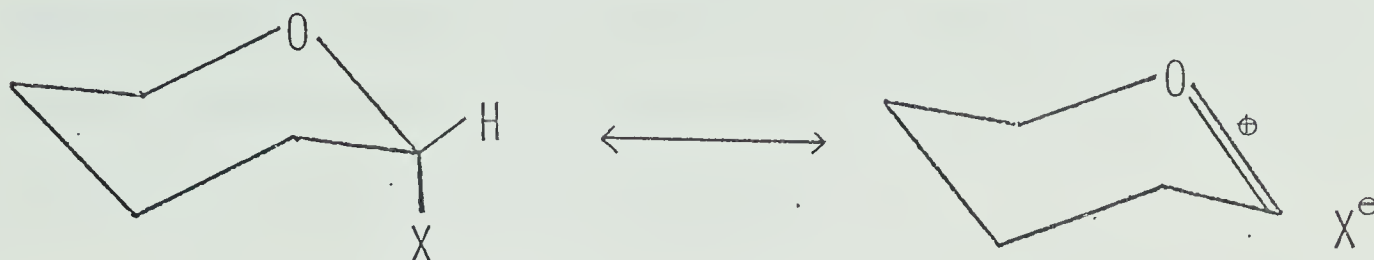
Influence of the C₅-substituent (R) on the anomeric effect



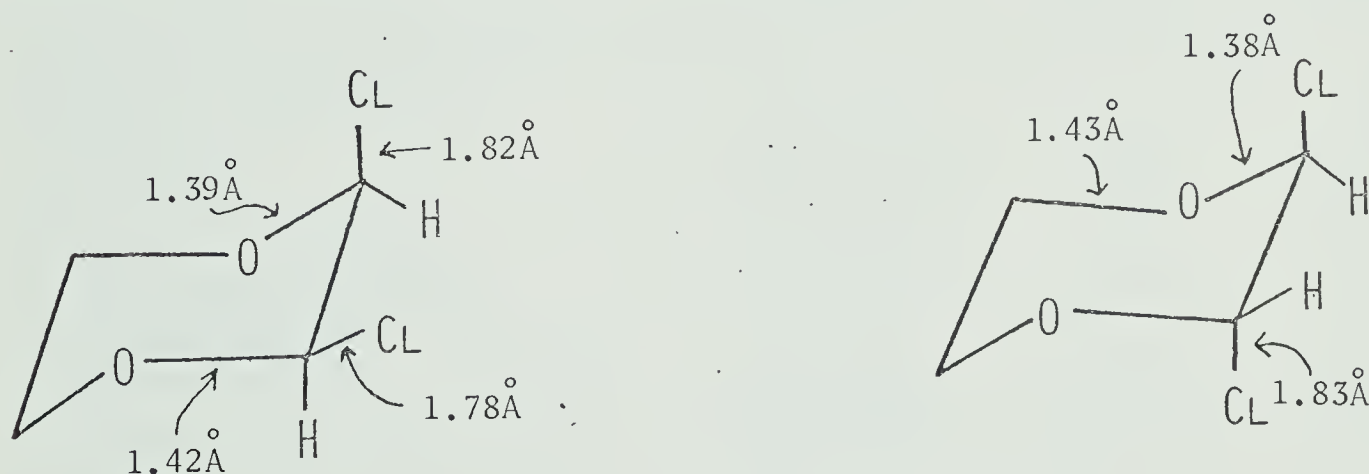
R	Anomeric effect kcal/mole
H	1.27
CH ₃	1.28
CH ₂ I	1.32
CH ₂ Cl	1.40
CH ₂ OAc	1.42
CH ₂ OTs	1.75

It is evident from the above table that an increase in the electronegativity of the C₅-substituent increases the anomeric effect.

Altona (42,46,51) proposed that the resonance stabilization of the axial anomer results from the double bonding of the ring oxygen to C₁. The experimental basis for his proposal was derived from the X-ray



crystallographic analyses of the dichloro dioxanes which show C-O bond shortening and C-Cl bond lengthening when the chlorine atom is in the axial orientation. Altona (56) also obtained evidence from the dipole



moment studies that this is also the case for these compounds in solution.

In recent years a number of carbohydrate molecules have been subjected to X-ray crystal structure analysis to gain insight into the shape of these molecules in the solid state. Sundaralingam (4) has recently discussed the stereochemistry and hydrogen bonding of

carbohydrates. The carbohydrates and gem-diols have one thing in common; they have two oxygen atoms attached to the same saturated carbon atom (anomeric and geminal carbon atoms). Sundaralingam (57) pointed out that in such compounds, bond shortening of C-O bond distances involving the carbon atom is observed. The C₁-O₁ bond distance is significantly shortened from the normal C-O bond distance [a value of 1.428 Å (58) is normally associated with a C-O single bond distance] in both the anomers of sugars. The data are reproduced in Table 3.

TABLE 3
C-O Distances in the C₅-O₅-C₁-O₁ (H) system

	C-O Distance, Å ^a		
	C ₁ -O ₁	C ₁ -O ₅	C ₅ -O ₅
Equatorial anomers			
β-D-Glucose	1.404(0.010)	1.437	1.455
Cellobiose (ring B)	1.381(0.007)	1.435	1.437
K β-D-Glucuronate·2H ₂ O	1.413(0.011)	1.408	1.446
Ba β-D-Glucose-6-phosphate·7H ₂ O	1.416(0.03)	1.397	1.439
β-Lyxose	1.364(0.006)	1.435	1.422
Axial anomers			
α-L-Rhamnose·H ₂ O	1.379(0.02)	1.420	1.456
α-D-Glucose	1.389(0.003)	1.425	1.427
β-L-Arabinose	1.382(0.02)	1.421	1.440
β-DL-Arabinose	1.392(0.001)	1.434	1.447
α-L-Sorbose	1.415(0.005)	1.420	1.410

^aEstimated standard deviations σ in parentheses.

However, unlike the gem-diols, the second C-O bond, viz. C₁-O₅, showed no significant difference from the normal value. Recently, Jeffrey and coworkers (59) observed the correlations between the anomeric C-O bond distances. These are as follows: in the case of equatorial glycopyranosides, the anomeric C₁-O₁ bond is significantly shortened when compared with the normal value, whereas the ring C-O bonds are about equal as the results reproduced in Table 4 show.

TABLE 4

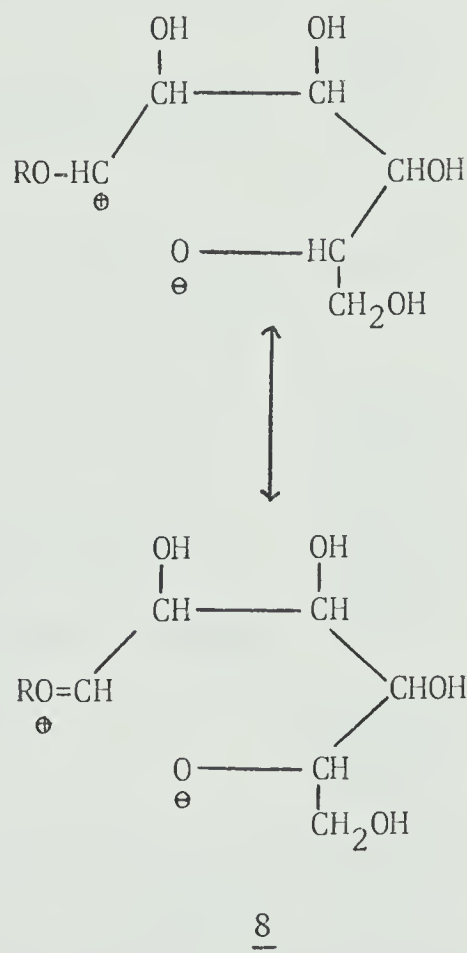
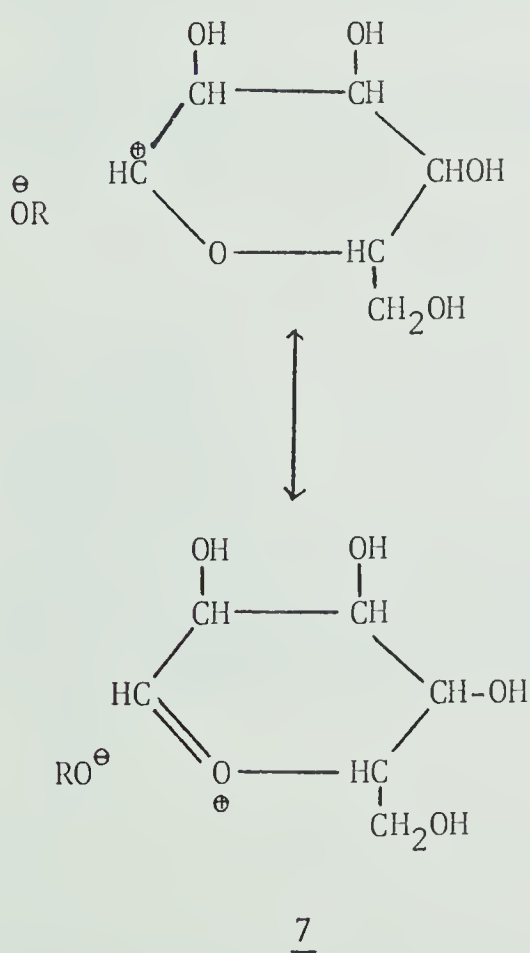
C-O Distances in the C₅-O₅-C₁-O₁-R system, where R = C^a

	C-O Distances, Å ^b			
	C ₁ -O ₁	C ₁ -O ₅	C ₅ -O ₅	C ^a -O ₁
Equatorial anomers				
Methyl-β-D-xyloside	1.390(0.003)	1.422	1.425	1.427
Cellobiose (ring A)	1.397(0.007)	1.425	1.436	1.446
Methyl-β-D-maltopyranoside (β-D-glucose residue)	1.375(0.007)	1.427	1.430	1.425
Axial anomers				
Methyl-6-bromo-6-deoxy-α-D-galactopyranoside	1.430(0.014)	1.421	1.461	1.436
Rb 6-sulfo-6-deoxy-α-D-glucopyranosyl-(1,1')-D-glycerol	1.379(0.014)	1.402	1.433	1.419
Sucrose (α-D-glucose residue)	1.420(0.003)	1.408	1.436	1.428
Cyclohexaamylose potassium acetate	1.398(0.011)	1.426	1.445	1.443
	G2	1.410(0.011)	1.417	1.451
	G3	1.417(0.011)	1.439	1.403
Methyl-β-D-maltopyranoside (α-D-glucose residue)	1.416(0.007)	1.408	1.440	1.438
Methyl-α-D-glucoside	1.410(0.001)	1.413	1.433	

^bEstimated standard deviations σ in parentheses.

On the other hand, there is significant difference in the ring C-O bond distances in the case of axial glycopyranosides. The C_1-O_5 bond seems to possess double bond character, whereas C_1-O_1 bond distance is slightly shorter than normal. Thus, it was inferred that in general one or both C-O bonds associated with the common carbon atom possess double bond character, whereas there was slight bond lengthening of the C-O bond not involving the common carbon when compared with normal single bond length.

Sundaralingam (4) suggested the double bond-no bond resonance structure of the following type (similar to Altona's proposals) to explain some of the C-O bond shortening effects.



The drawback with the resonance theory is that it does not explain the increase in the anomeric effect with the increase in the

electronegativity of the substituent at C₅ as described earlier.

Sundaralingam (4) made an interesting observation about the differences in the O₁-C₁-O₅ angles and the intramolecular O₁ . . . O₅ distance in the anomeric pyranosides. The results reproduced in Table 5

TABLE 5

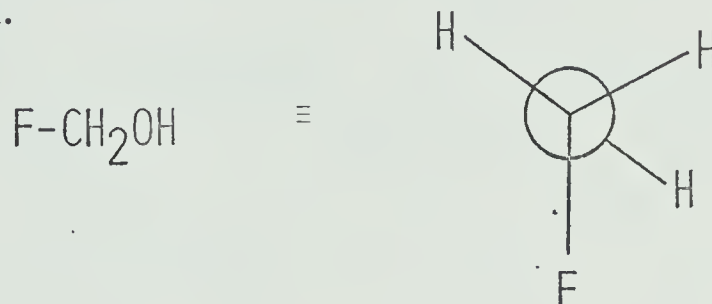
Comparison of the O₁-C₁-O₅ angles and the intramolecular O₁ . . . O₅ distances in the anomeric glycopyranosides

Anomers	O ₁ C ₁ O ₅ Angle	O ₁ ...O ₅ Distance, Å
Equatorial anomers		
β-D-Glucose	106.0°	2.269
K β-D-Glucuronate	108.3°	2.287
Ba β-D-Glucose-6-phosphate·7H ₂ O	106.0°	2.247
Cellobiose		
Ring A	107.0°	2.274
Ring B	107.4°	2.270
Methyl-β-D-maltopyranoside (β-D-glucose residue)	107.1	2.254
Methyl-β-D-xyloside	107.0°	2.261
Average	107.0°	2.266
Axial anomers		
α-D-Glucose	111.5°	2.326
β-L-Arabinose	113.0°	2.337
β-DL-Arabinose	112.9°	2.355
α-L-Sorbose	110.2°	2.325
Methyl-6-bromo-6-deoxy-α-D-galactopyranoside	110.3°	2.340
Sucrose (α-D-glucose residue)	110.7°	2.326
Methyl-β-D-maltopyranoside (α-D-glucose residue)	111.5°	2.334
Cyclohexaamylose potassium acetate		
G1	111.0°	2.327
G2	111.9°	2.342
G3	110.9°	2.352
Average	111.4°	2.336

show that the average value is 111.3° for the angle, O₁-C₁-O₅ for the axial anomer which is greater than the tetrahedral value and also 4°

greater than that of the equatorial anomer. On the other hand the intramolecular $O_1 \cdots O_5$ distance is $0.07 \text{ \AA}$ greater in the axial anomer as compared with the equatorial anomer. It could be concluded that $O_1 \cdots O_5$ non-bonded interaction is less in the case of the axial anomer than the equatorial anomer.

Wolfe and coworkers (54) who call the Anomeric Effect "The Edward-Lemieux Effect" examined it theoretically by an *ab initio* calculation using fluoromethanol as a model compound. The stable conformation had the C-F bond *trans* to one "electron-pair" and *gauche* to another. The conformation in which the C-F bond bisected the "electron pairs" was the energy maximum.



These authors concluded that the Edward-Lemieux Effect exhibited by fluoromethanol could be discussed generally in terms of interactions of *bonded* electron pairs with each other. As is shown in the following structures, the C_5-O bond corresponds to the O-H bond of fluoromethanol



and the C-X bond corresponds to the C-F bond of fluoromethanol, the anomeric effect arises because of the way in which the interactions between these bonds are balanced. This corresponds closely to Lemieux and Chü's (13,17) original conception of the anomeric effect.

In view of more favorable intramolecular dipole-dipole interactions likely being present in the axial anomer as compared to that in the β -anomer, the magnitude of the anomeric effect would be expected to vary inversely with the dielectric constant of the solvent. Lemieux and coworkers (21) studied the effect of solvent polarity on the conformational equilibrium for 4,4,5,5-tetradeuterio-2-methoxy-tetrahydropyran by n.m.r. spectroscopy. The incorporation of deuterium at C₄ and C₅ was necessitated to eliminate the virtual coupling of H₂ with the hydrogens at the 4-position which were only weakly chemically shifted from those at the 3-position. These results are reproduced in Table 6.

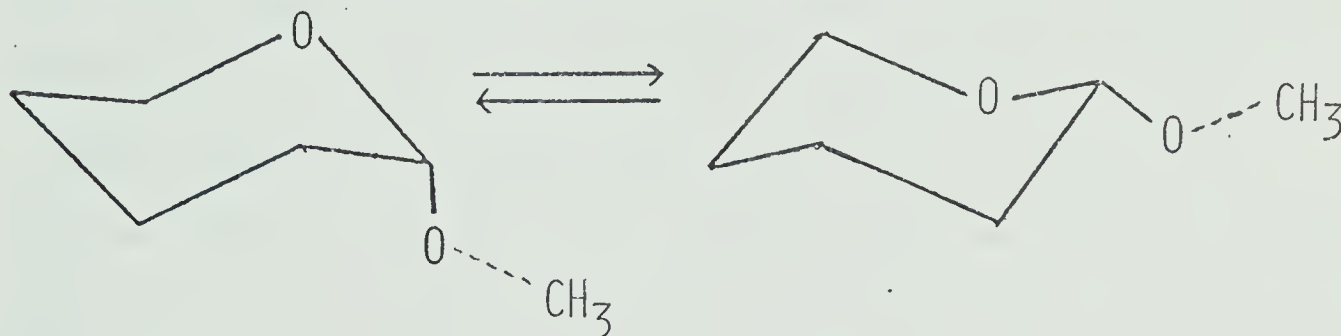


TABLE 6

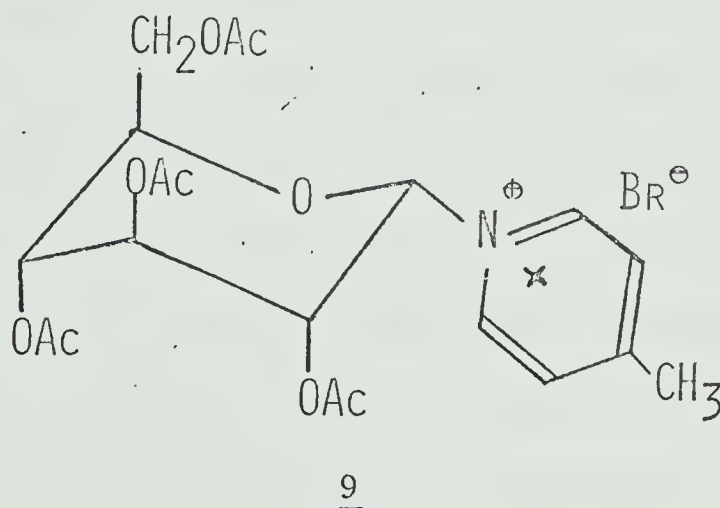
Effect of solvent on the chair-chair equilibrium
for 2-methoxy-tetrahydropyran

Solvent	Dielectric constant	% Equatorial form
CCl ₄	2.2	17
C ₆ D ₆	2.3	18
CS ₂	2.6	20
(CD ₃) ₂ SO	36	26
CDCl ₃	4.8	29
CH ₃ OD	32	31
CD ₃ CN	38	32
D ₂ O	78	48

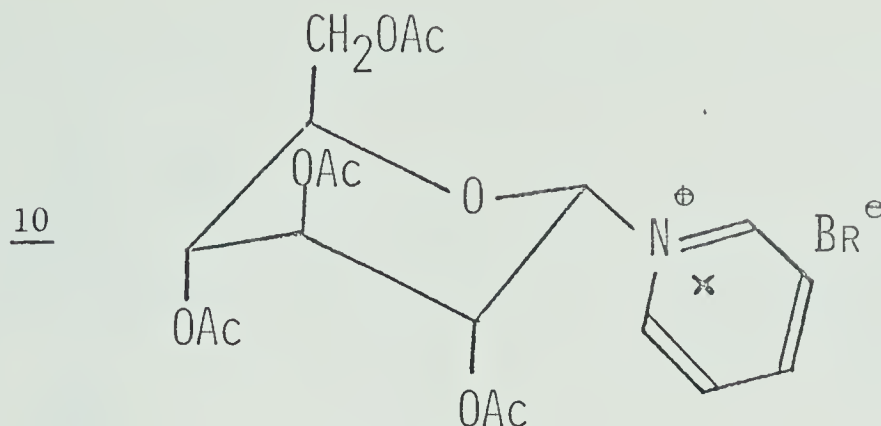
It is evident from the above table that the higher the dielectric constant of the solvent, the higher is the population of the more polar equatorial form present at equilibrium.

B. The Reverse Anomeric Effect

In 1965, Lemieux and Morgan (60) found from the n.m.r. studies of N-(Tetra-*O*-acetyl- α -D-glucopyranosyl)-4-methyl pyridinium bromide (9), that the compound has the pyranose ring strongly distorted from the 4C_1 conformation (61). The observed coupling constants, $J_{1,2} = 2.8$, $J_{2,3} = 3.1$, $J_{3,4} = 3.2$ and $J_{4,5} = 5.7$ Hz, suggested a nearly equatorial orientation for the pyranose ring protons (H_2 to H_4). Furthermore, the chemical shifts of three of the four *O*-acetyl protons were indicative of axial orientation for these substituents (5). In view of the observed coupling constants, these authors suggested that the compound appeared to have a conformation which is close to the 1C_4 conformation as shown below:

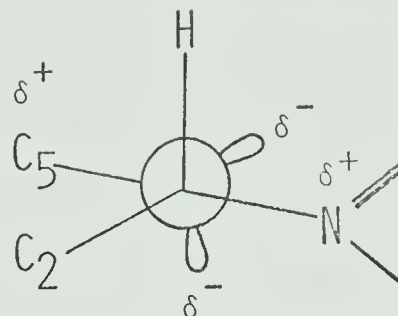
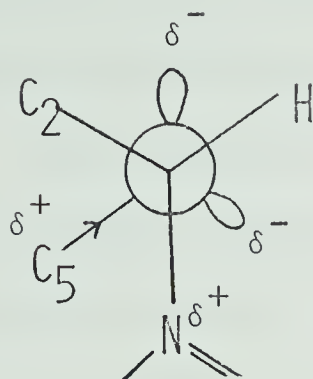


Lemieux and Morgan (62) also found that the structurally related N-(tetra-*O*-acetyl- α -D-glucopyranosyl)-pyridinium bromide (10) gave a virtually identical n.m.r. spectrum in water with that of 9, suggesting that it exists in a conformation approaching the 1C_4 conformation.



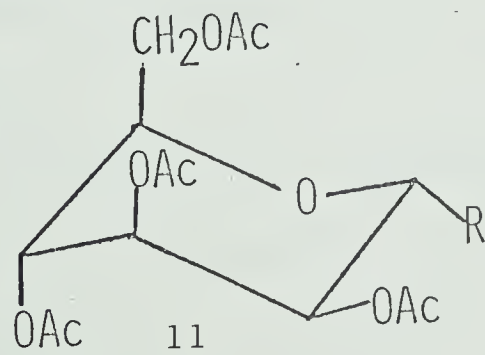
Recently James (63), through X-ray crystallographic studies, has shown that compound 9 exists in the boat ($^{2,5}_B$) conformation and this finding shall be discussed later in more detail. Incidentally, the 1C_4 conformation is only a distortion of the $^{2,5}_B$ conformation.

Such a strong distortion of the pyranose ring from the 4C_1 conformation could at first be thought to arise from a powerful non-bonded interaction arising from the pyridinium group in the axial orientation at the anomeric center. The A value for the benzene ring is believed to be in the order of only 2-3 kcal/mole (64) and hence the distortion noted in 9 and 10 could not have been expected on steric grounds alone, although the C-N bond lengths in quaternary ammonium compounds is shorter by about 0.04 Å than the C-C bond in a compound such as toluene (65). These authors argued that the establishment of a positively charged atom in the axial orientation must meet a strongly destabilizing effect (relative to when the group is in the equatorial orientation) arising from the electrostatic interaction between the C₁ to N and C₅ to O₅ bonds, when the nitrogen and C₅ atoms are in *gauche* relationship.



Since the polarity of the C_1 -aglycon bond is now reversed, the aglycon prefers the equatorial orientation. Lemieux and Morgan (60) named this as the "Reverse Anomeric Effect." In adopting the 1C_4 or ${}^{2,5}B$ conformation, the compounds 9 and 10 experience strong steric interactions from the axial orientations of acetoxy groups. From this, one could safely conclude that the reverse anomeric effect overrides the steric interactions. It should also be noted that the steric interaction of the pyridinium group in the 4C_1 conformation of 9 and 10 is released in the ${}^{2,5}B$ conformation.

Similar observations of this nature have been made by other workers. Onodera, Hirano, Masuda and Kashimura (66) reported that the tetra-*O*-acetyl- α -D-mannopyranosyl theophylline (11) exists in 1C_4 conformation.



R = THEOPHYLLINE

Recently Onodera and coworkers (67) showed through n.m.r. spectroscopy that β -L-rhamnopyranosides and α -D-mannopyranosides of adenine and theophylline existed in a rapid equilibrium between the two chair

conformations, 4C_1 and 1C_4 in water, but only the 1C_4 conformation in DMSO- d_6 and pyridine- d_5 .

The importance of the Anomeric Effect studies and their contributions towards a better understanding of the chemical reactions at C_1 of carbohydrates have been a motivating stimulus behind the work presented herein. The Reverse Anomeric Effect has been examined by studying its effect on ring conformation equilibria arising from *N*-methylation or protonation of the imidazole ring of *N*-glucosides and mannosides. The advantage with imidazole nucleosides as compared with pyridinium compounds is that the ring size of imidazole remains nearly the same before and after protonation or *N*-methylation, thus avoiding any serious steric interactions. That a quaternized nitrogen at the anomeric position of a lactol ring structure strongly favors an equatorial orientation, could be of great importance towards the understanding of the conformational changes that occur during essential biochemical reactions of pyridine nucleosides (60). The present work also includes *N*-ribofuranosyl imidazoles as model compounds for pyrimidine and purine nucleosides, in an effort to assess the effects on conformation of either protonation or conjugation of the anomeric nitrogen with the neighboring oxygen.

For this research, n.m.r. spectroscopy was an essential tool for the characterization of products both as to structure and conformation (6,7). In the present work, the calculation of dihedral angles from the observed coupling constants was based on the general expression (68,69).

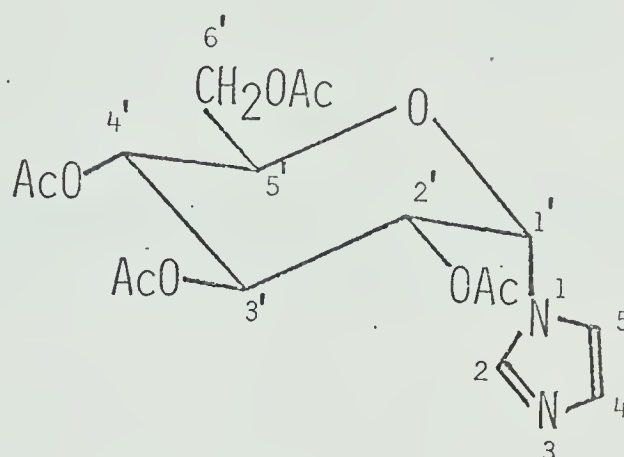
$$J = x \cos^2 \phi + y$$

The empirical parameters x and y were introduced to account for the special structural properties of cyclohexane and pyranose rings (70). It was realized that the Karplus parameters are subject to a substituent effect, and empirical modifications of the Karplus parameters were developed to allow for the different carbohydrate molecules under consideration (71,72). Care has to be taken not to interpret the available data too rigorously, since it is known that the coupling constants are also subject to electronegativity and other effects (69,73,74). Lemieux and coworkers (72), from an analysis of the spectrum of 1,3-dioxolane, suggested that the Karplus curve should be subjected to an upward displacement of 2.2 Hz. This modification has the merit of rationalizing the common occurrence of axial:axial coupling constants larger than the maximum of 9.2 Hz corresponding to the original Karplus parameters. Throughout this study, this modified Karplus curve (72) will be used for all the ring protons other than the anomeric proton. Since the anomeric carbon atom usually carries two electronegative substituents, the proton attached to this center may be considered a special case meriting a different Karplus equation. James (75) has found using X-ray crystallography that the chair conformation of tetra-*O*-acetyl- α -D-glucopyranosyl chloride deviates from the ideal chair to an extent of 10-16° variation in the dihedral angles, the angle between H_1 and H_2 being approximately 165°. If glycopyranosyl imidazoles have $\phi_{H_1'}, H_2'$ of the same magnitude and the observed $J_{1',2'}$ for 1-(β -D-glucopyranosyl)-imidazole (to be described later) in this study is 8.5 Hz (H_1' and H_2' are *trans* diaxial), the following Karplus equation may be used to describe the H_1 coupling constants throughout

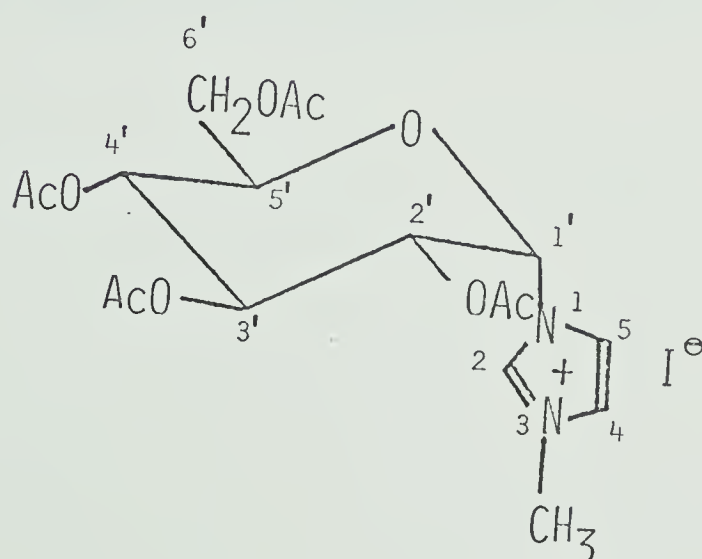
this study:

$$J_{\phi} = 9.4 \cos^2 \phi - K$$

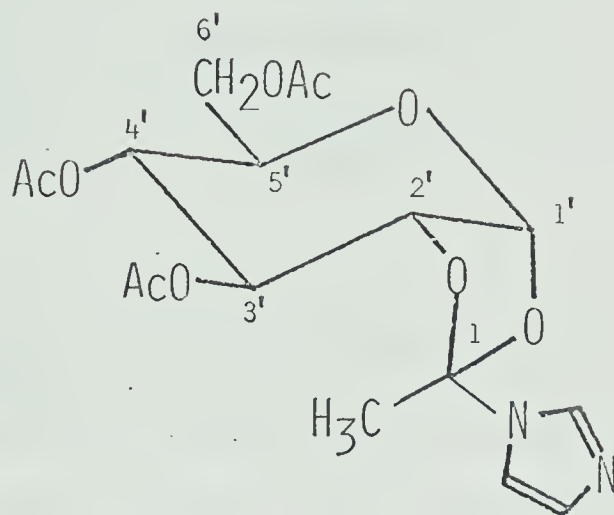
The numbering system to be used in this presentation is as follows: numerals will designate positions on the base and the primed numerals, positions on the sugar ring, as shown below:



1-(Tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole



3-Methyl-1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazolium Iodide



3',4',6'-Tri-*O*-acetyl-1',2'-*O*-(1-*exo-N*-imidazolyl ethylidene)- α -D-glucopyranose

The term *endo*- and *exo*- are used to designate the configuration at the asymmetric C-atom, C₁, in the dioxolane ring. The isomer with the imidazole group *trans*- to the pyranose ring will be termed the *exo*-orthoamide.

II EXPERIMENTAL

A. Materials

1. Solvents

- (i) Acetonitrile: Reagent grade acetonitrile was dried over phosphorus pentoxide and distilled under anhydrous conditions.
- (ii) Triethylamine: Reagent grade triethylamine was dried by storage over potassium hydroxide pellets.
- (iii) Chloroform: Reagent grade chloroform was freed from the ethanol stabilizer by passing through a column of activated alumina just before use (76).
- (iv) 1,2-Dichloroethane: Reagent grade 1,2-dichloroethane was redistilled and stored over molecular sieves.

2. Reagents

- (i) Tetra-*n*-butylammonium Bromide: Tetra-*n*-butylammonium bromide was prepared, by heating under reflux for 36 h, equimolar amounts of *n*-butylbromide and tri-*n*-butylamine in acetonitrile (77). The crystalline product obtained after removal of the solvent *in vacuo* was recrystallized from ethyl acetate and dried over phosphorus pentoxide *in vacuo*. The compound melted at 106°.
- (ii) Silica Gel G: Silica Gel G employed for thin layer chromatography contained about 13% calcium sulfate binder and was purchased from E. Merck A.G., Darmstadt, W. Germany.
- (iii) Silicic Acid: Silicic acid (100 mesh) used for column Chromatography was supplied by Mallinckrodt Chemical Works, St. Louis, Mo., U.S.A.

- (iv) Imidazole: Commercial imidazole was not purified prior to use.
- (v) Trifluoroacetic Acid: Commercial product was used as received.
- (vi) Methyl Iodide: Commercial methyl iodide was redistilled prior to use.
- (vii) Tetra-O-acetyl- α -D-glucopyranosyl Bromide (12)

This compound was prepared according to the procedure described by Lemieux (78). The physical constants, m.p. 87.5-88.5°; $[\alpha]_D +196^\circ$ (*c*, 2 in chloroform) were in good agreement with those reported [(78) m.p. 88-89°, $[\alpha]_D +198^\circ$ (*c*, 2 in chloroform)].

- (viii) Tetra-O-acetyl- α -D-mannopyranosyl Bromide (25)

This compound was prepared by a procedure similar to that described for the preparation of the corresponding *gluco*-isomer (78). However, the product could not be induced to crystallize. The n.m.r. spectrum in deuteriochloroform was identical to that of a sample of the same compound prepared by Lemieux and Earl (79).

B. Methods

1. Chromatography

(i) Thin Layer Chromatography (t.l.c.): Thin layer chromatography was performed on Silica Gel G (see p. 25). Chloroform-acetone (80:20) was used as the developing solvent for the acetylated compounds and ethylacetate-pyridine-water (8:2:1) for the deacetylated compounds. The spots were detected by spraying with 20% sulfuric acid and heating on a hot plate.

(ii) Column Chromatography: Column chromatography was carried out on columns of silicic acid (100 mesh). The fractions were collected by a

mechanical fraction collector. Individual fractions were examined both by optical rotation and thin layer chromatography.

2. Optical Rotation: These were measured with a Perkin-Elmer automatic polarimeter, Model 141.

3. Melting Point: Melting points were determined in capillary tubes with a Gallenkamp Melting Point Apparatus and are uncorrected.

4. Spectroscopic Data: Nuclear magnetic resonance spectra were measured at 60 MHz with a Varian A60 or A-56/60A spectrometer. Spectra at 100 MHz were measured with a Varian HA 100 spectrometer and at 220 MHz were measured at Ontario Research Foundation, Sheridan Park, Ontario (Canadian 220 MHz NMR Centre). Chemical shifts are reported in *tau* (τ) values (estimated error ± 0.05 p.p.m.) and refer to resonance signals relative to tetramethyl silane (TMS) used as either internal or external standard depending on the solvent used. When necessary double resonance experiments were performed to confirm the assignments of signals and facilitate the measurement of the coupling constants (estimated error ± 0.5 Hz) using a frequency sweep technique. Whenever necessary the relative concentrations of the components in a mixture were obtained from the n.m.r. spectrum by direct comparison of peak areas of known signals.

C. Synthetic Investigation

1. 1-(Tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20) and the β -Anomer (21)

Tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), 4.11 g (10 mmoles), imidazole, 1.36 g (20 mmoles), and tetra-*n*-butylammonium bromide, 3.22 g (10 mmoles), were dissolved in anhydrous acetonitrile, 20 ml. The mixture was heated on a steam bath under reflux for 4 h. Acetonitrile was removed *in vacuo* and the residue dissolved in chloroform, 50 ml. The chloroform solution was freed from salts such as imidazole hydrobromide and tetra-*n*-butylammonium bromide by washing thoroughly with water and then dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* left a residue which on t.l.c. examination showed the presence of five components. This residue was then subjected to column chromatography. A saturated solution of the residue was placed on top of a column (diameter, 3 cm) packed with silicic acid, 150 g (100 mesh). The elution was carried out with 20% acetone in chloroform and the eluent was collected using a mechanical fraction collector (15 ml).

The first fraction contained a 3:1 mixture of tetra-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enopyranose (22) and 1,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose (18). From the n.m.r. spectrum of the mixture the following data were obtained; for the compound 18: τ 3.65 (1-proton, doublet, H_1 , $J_{1,2}$ 3.2 Hz) and for the compound 22: τ 3.33 (1 proton, singlet, H_1), 4.40 (1 proton, doublet, H_3 , spacing 4 Hz). These were consistent with the corresponding n.m.r. data already reported for the compounds 18 and 22 (80,81). The second fraction contained

2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose (19), the n.m.r. spectrum of which was identical with that reported by Detert (80). The overall yield of 22 varied between 7 to 10%, as was the combined yield of the two tetraacetates, 18 and 19.

1-(Tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20) was obtained as the third fraction; 25% recovered yield. Crystallization from ethanol gave 20, m.p. 172-173°, $[\alpha]_D^{25} +111^\circ$ (*c*, 2 in chloroform) and its n.m.r. spectrum is reproduced in Fig. 6 and the parameters are presented in Table 9.

Anal. Calcd. for $C_{17}H_{22}O_9N_2$: C, 51.25; H, 5.57; N, 7.03%.

Found: C, 51.26; H, 5.77; N, 7.1%.

The last fraction from the column contained 1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21); 30% recovered yield. Crystallization from ethanol furnished 21, m.p. 218-220° [reported (82) 205-208°], $[\alpha]_D^{25} -9^\circ$ (*c*, 1 in chloroform), and its n.m.r. spectrum is reproduced in Fig. 9.

N.m.r. data: τ 4.72 (4-protons, singlet, H_1' , H_2' , H_3' , and H_4').

Anal. Calcd. for $C_{17}H_{22}N_2O_9$: C, 51.25; H, 5.57; N, 7.03%.

Found: C, 51.04; H, 5.32; N, 6.97%.

1-(Tetra-*O*-acetyl-D-glucopyranosyl)-imidazole was prepared according to the method of Bergman and Heimhold (82). The product was crystallized from ethanol, m.p. 217° [reported (82) 205-08°].

N.m.r. data: τ 4.72 (4 protons, singlet, H_1' , H_2' , H_3' , and H_4').

2. 3-Methyl-1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazolium
Iodide (44)

1-(Tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20), 398 mg (1 mmole), was dissolved in dry acetonitrile, 2 ml, and methyl iodide, 1 ml (excess), was added. The solution was refluxed on a steam bath for 2 h. The solvents were then removed by evaporation under diminished pressure and the residue dried *in vacuo* to yield a light yellow powder, 540 mg (100%). Although the compound, $[\alpha]_D^{25} \approx +53^\circ$ (*c*, 1 in chloroform) failed to crystallize, the elemental analysis indicated it to be of high purity. The n.m.r. spectrum of this compound is reproduced in Fig. 8 and the parameters are presented in Table 12.

Anal. Calcd. for $C_{18}H_{25}N_2O_9I$: C, 40.00; H, 4.63; N, 5.18; I, 23.52%. Found: C, 39.77; H, 4.82; N, 5.37; I, 23.58%.

3. 3-Methyl-1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazolium
Iodide (46)

1-(Tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21), 398 mg (1 mmole), was dissolved in anhydrous acetonitrile, 2 ml. To this solution was added methyl iodide, 1 ml, and the mixture was heated on the steam bath for 2 h. The excess of methyl iodide and acetonitrile were removed by evaporation under diminished pressure and the residue dried *in vacuo*. The weight of the product thus obtained was 540 mg, indicating the consumption of one mmole of 21 and one mmole of methyl iodide. The residue when dissolved in methanol afforded crystals, m.p. 217-218°, $[\alpha]_D^{25} -11^\circ$ (*c*, 1 in chloroform). The n.m.r. spectrum of 3-methyl-1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazolium iodide (46) is reproduced in Fig 11 and the parameters are presented in Table 13.

Anal. Calcd. for $C_{18}H_{25}N_2O_9I$: C, 40.00; H, 4.63; N, 5.18%.

Found: C, 40.22; H, 4.58; N, 5.07%.

4. 1-(α -D-Glucopyranosyl)-imidazole (49)

1-(Tetra-O-acetyl- α -D-glucopyranosyl)-imidazole (20), 2.0 g, was dissolved in a mixture of methanol and water (1:1), 40 ml. To this solution was added triethylamine, 8.3 ml, and the reaction mixture was allowed to stand overnight at room temperature. Then the solvents were evaporated under diminished pressure and the residue was dried *in vacuo*. The residue when dissolved in ethanol afforded 1.1 g (90%) of 49, m.p. 101°, $[\alpha]_D^{25} +104^\circ$ (*c*, 2 in water). The n.m.r. spectrum of 49 is reproduced in Fig 17 and the parameters are presented in Table 19

Anal. Calcd. for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17%.

Found: C, 47.05; H, 6.26; N, 12.37%.

5. 3-Methyl-1-(α -D-glucopyranosyl)-imidazolium Iodide (50).

1-(α -D-Glucopyranosyl)-imidazole (49), 0.5 g, was suspended in anhydrous acetonitrile, 5 ml, and to this mixture added methyl iodide, 2 ml. The mixture was heated on the steam bath for 5 h. The solvents were then removed by evaporation *in vacuo*. This gave a quantitative yield of a residue which when dissolved in methanol and allowed to stand in refrigerator, afforded crystals, m.p. 170-172°, $[\alpha]_D^{25} +82^\circ$ (*c*, 1 in water). The n.m.r. spectrum of 50 is reproduced in Fig. 18 and the parameters are presented in Table 20.

Anal. Calcd. for $C_{10}H_{17}N_2O_5I$: C, 32.25; H, 4.57; N, 7.52%.

Found C, 31.98; H, 4.86; N, 7.78%.

6. 1-(β -D-Glucopyranosyl)-imidazole (51).

1-(Tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21), 2.0 g, was dissolved in a mixture of methanol-water (1:1), 40 ml. To this solution was added triethylamine, 8.3 ml, and the solution was allowed to stand overnight at room temperature. The solvents were then removed by evaporation under diminished pressure and the residue dried *in vacuo*. The residue when dissolved in ethanol afforded 0.9 g (78%) of 51, m.p. 227-228° [reported (82) 217°], $[\alpha]_D^{25} +1^\circ$ (*c*, 1 in water), the n.m.r. spectrum of which is reproduced in Fig. 19.

N.m.r. data: τ 4.25 (1 proton, doublet, $H_{1'}$, $J_{1',2'}$ 8.5 Hz).

Anal. Calcd. for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17%.

Found: C, 46.95; H, 6.28; N, 12.49%.

7. 3-Methyl-1-(β -D-glucopyranosyl)-imidazolium Iodide (52).

1-(β -D-Glucopyranosyl)-imidazole (51), 1.0 g, was suspended in anhydrous acetonitrile, 10 ml, and to this was added methyl iodide, 4 ml. The mixture was heated on the steam bath for 5 h. The solvents were then removed by evaporation under diminished pressure and the residue dried *in vacuo*, 1.6 g (100%). When dissolved in methanol and allowed to stand in the refrigerator, the residue afforded 52, m.p. 172°, $[\alpha]_D^{25} +16^\circ$ (*c*, 1 in water), the n.m.r. spectrum of which is reproduced in Fig. 20.

N.m.r. data: τ 3.95 (1 proton, multiplet, $H_{1'}$, with a width of 8.8 Hz) and 5.48 (3 proton, singlet, N-CH₃).

Anal. Calcd. for $C_{10}H_{17}N_2O_5I$: C, 32.25; H, 4.57; N, 7.52%.

Found: C, 32.15; H, 4.74; N, 7.53%.

8. Tri-*O*-acetyl-1',2'-*O*-(1-*exo-N*-imidazolyl ethylidene)- α -D-glucopyranose (23)

Tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), 4.11 g (10 mmoles), imidazole, 1.36 g (20 mmoles), tetra-*n*-butylammonium bromide, 3.22 g (10 mmoles), and triethylamine, 1.38 ml (10 mmoles), were dissolved in anhydrous acetonitrile, 20 ml. The reaction mixture was allowed to stand at room temperature. Thin layer chromatographic examination indicated that the reaction was essentially complete in 5 h. Then the solvents were removed under diminished pressure and the residual syrup dissolved in chloroform, 50 ml. The chloroform solution was thoroughly washed with water, and then dried over anhydrous sodium sulfate. The chloroform was evaporated under diminished pressure and the residue dried *in vacuo*. The n.m.r. spectrum of the residue showed it to consist of tri-*O*-acetyl-1',2'-*O*-(1-*exo-N*-imidazolyl ethylidene)- α -D-glucopyranose (23) ($\sim 77\%$), tetra-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enopyranose (22) ($\sim 14\%$), and a mixture of α - and β -*N*-glucosides, 20 and 21 ($\sim 9\%$). To a saturated solution of the residue in chloroform was added, dropwise, Skelly Solve "C" until the solution turned turbid and then it was left at room temperature. The precipitate which resulted was collected by filtration, washed with Skelly Solve "C" and dried *in vacuo*. Crystallization from anhydrous diethyl ether afforded 23, m.p. 131-132°, $[\alpha]_D^{25} +48^\circ$ (*c*, 2 in chloroform), the n.m.r. spectrum of which is shown in Fig. 4.

N.m.r. data: τ 4.34 (1 proton, doublet, $H_{1'}$, $J_{1',2'}$ 5.2 Hz), 4.84 (1 proton, triplet, $H_{3'}$, $J_{2',3'}$ 2.6 Hz, $J_{3',4'}$ 2.4 Hz), 5.14 (1 proton; broad quartet, $H_{4'}$, $J_{4',5'}$ 9 Hz).

Anal. Calcd. for $C_{17}H_{22}N_2O_9$: C, 51.25; H, 5.57; N, 7.03%.

Found: C, 51.16; H, 5.42; N, 7.05%.

9. Imidazole Hydrobromide

Imidazole, 1.0 g, was dissolved in methylene chloride, 10 ml, and the solution cooled to 0°. Anhydrous hydrogen bromide gas was passed through the solution for 5 min. The white precipitate produced was isolated by filtration and washed with methylene chloride. Crystallization from ethanol gave a near quantitative yield of imidazole hydrobromide, m.p. 225-226°.

Anal. Calcd. for $C_3H_5N_2Br$: C, 24.16; H, 3.60; N, 18.74%.

Found: C, 24.46; H, 3.72; N, 18.41%.

10. 1-(Tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20) and 1-(Tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21) from Tri-*O*-acetyl-1',2'-*O*-(1-*exo-N*-imidazolyl ethylidene)- α -D-glucopyranose (23)

A solution of tri-*O*-acetyl-1',2'-*O*-(1-*exo-N*-imidazolyl ethylidene)- α -D-glucopyranose (23), 3.98 g (10 mmoles), and imidazole hydrobromide, 1.48 g (10 mmoles), in acetonitrile, 20 ml, was heated under reflux for 4 h. The acetonitrile was then removed under diminished pressure and the residual syrup dissolved in chloroform, 50 ml. The chloroform solution was thoroughly washed with water and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* left a residue, the t.l.c. of which showed the presence of five components. The residue was consequently subjected to column chromatography (150 g, silicic acid; column diameter, 3 cm). The following compounds were isolated: 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20) (25%);

1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21) (30%); 1,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose (18) and 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose (19) (combined yield *ca.* 7-10%) and tetra-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enopyranose (22) (10%). These products were all characterized by n.m.r. spectroscopy.

11. A Study of the Reactions of Tetra-*O*-acetyl- α -D-glucopyranosyl Bromide (12) with Imidazole.

(i) Tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), 1.027 g (2.5 mmoles), imidazole, 0.34 g (5 mmoles), and tetra-*n*-butylammonium bromide, 0.805 g (2.5 mmoles), were dissolved in anhydrous acetonitrile, 5 ml. The reaction mixture was allowed to stand at room temperature and its progress was monitored by t.l.c. After 5 h, all the starting material 12 had reacted. After a work-up similar to that previously described, a residue was obtained, the n.m.r. spectrum of which showed it to consist mainly of the orthoamide 23 ($\sim$ 80%) and 22 ($\sim$ 5%). The remaining 15% consisted of α - and β -*N*-glucosides 20 and 21, respectively, and the tetra-*O*-acetyl- α -D-glucopyranoses, 16 and 17.

(ii) Tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), 1.027 g (2.5 mmoles), imidazole, 0.34 g (5 mmoles), tetra-*n*-butylammonium bromide, 0.805 g (2.5 mmoles), and triethylamine, 0.35 ml (2.5 mmoles), were mixed in anhydrous acetonitrile, 5 ml. A clear solution produced was allowed to stand at room temperature. After 5 h, all the bromide 12 had reacted (t.l.c.) The n.m.r. spectrum of the residue, after a normal work-up, showed it to be a mixture of the orthoamide 23 ($\sim$ 77%), 22 ($\sim$ 14%) and the remaining 9% was a mixture of compounds 20, 21, 18 and 19.

(iii) Tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), 1.027 g (2.5 mmoles), imidazole, 0.34 g (5 mmoles), tetra-*n*-butylammonium bromide, 0.805 g (2.5 mmoles), and triethylamine, 0.35 ml (2.5 mmoles), were dissolved in anhydrous acetonitrile, 5 ml. The reaction mixture was heated under reflux. As was shown by n.m.r. monitoring of the reaction, it took 20 h for the orthoamide to disappear completely. At the same time n.m.r. spectrum also showed the presence of α - and β -N-glucosides 20 and 21. After a work-up similar to that previously described, a residue was obtained which was fractionated through column chromatography (column diameter, 2 cm and silicic acid, 50 g). The fractions isolated were: α -N-glucoside 20 (25%), β -N-glucoside 21 (30%) and tetra-*O*-acetates 18 and 19 (10% combined yield).

(iv) Tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), 1.027 g (2.5 mmoles), imidazole, 0.304 g (5 mmoles), were dissolved in anhydrous acetonitrile, 5 ml, and the reaction mixture was allowed to stand at room temperature for 5 h. The n.m.r. spectrum was determined on the residue resulting from a normal work-up, which showed it to be a 1:1 mixture of the starting material 12, τ 3.40 (1 proton, doublet, H_1 , $J_{1,2}$ 3.8 Hz) and the orthoamide 23, τ 4.34 (1 proton, doublet, H_1' , $J_{1',2'}$ 5.2 Hz).

(v) Tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), 1.027 g (2.5 mmoles), imidazole, 0.304 g (5 mmoles), were dissolved in anhydrous acetonitrile, 5 ml, and the reaction mixture allowed to stand at room temperature. After 12 h all the starting material had reacted (t.l.c.) and a normal work-up of the reaction mixture gave a residue, the n.m.r. spectrum of which showed it to consist of the orthoamide 23 ($\sim$ 80%) and

tetra-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enopyranose (22) (10%).

(vi) Tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), 1.027 g (2.5 mmoles), imidazole, 0.34 g (5 mmoles), tetra-*n*-butylammonium bromide, 0.805 g (2.5 mmoles), were dissolved in acetonitrile, 5 ml. The reaction mixture was heated under reflux for 4 h. After a normal work up, a residue was obtained which was subjected to column chromatography (column diameter, 2 cm and silicic acid, 50 g). The fractions isolated were: α -*N*-glucoside 20 (25%); β -*N*-glucoside 21 (30%); tetra-*O*-acetyl- α -D-glucopyranoses 18 and 19 (8%) and tetra-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enopyranose (22) (10%).

12. 1-(Tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32) and the β -Anomer (33)

Tetra-*O*-acetyl- α -D-mannopyranosyl bromide (25), 5.137 g (12.5 mmoles), and imidazole, 1.7 g (25 mmoles), were dissolved in anhydrous acetonitrile, 25 ml. The mixture was heated under reflux for 4 h. The acetonitrile was then removed *in vacuo* (water pump) and the residue dissolved in chloroform, 50 ml. The chloroform solution was washed several times with water to remove the salts and dried over anhydrous sodium sulfate. Removal of chloroform under diminished pressure left a syrupy residue, the t.l.c. of which showed it to be a mixture of four components. The residue was, therefore, subjected to column chromatography (column diameter, 3 cm and silicic acid, 175 g).

The first fraction collected was 1,3,4,6-tetra-*O*-acetyl- β -D-mannopyranose (29).

N.m.r. data: τ 3.95 (1 proton, doublet, H_1 , $J_{1,2} = 1$ Hz).

The second fraction was 2,3,4,6-tetra-*O*-acetyl- α -D-mannopyranose (31). The n.m.r. spectra for 29 and 31 were identical with the n.m.r. data already reported for these compounds (80). The total recovered yield of both tetra-acetates 29 and 31 was 10%.

1-(Tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32) was obtained in the third fraction as a syrup, in 30% recovered yield, $[\alpha]_D^{25} + 35^\circ$ (*c*, 2 in chloroform). The n.m.r. spectrum of 32 is reproduced in Fig. 12 and the parameters are presented in Table 14.

The last fraction collected from the column was 1-(tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazole (33) in 20% recovered yield. Although this compound failed to crystallize, the syrup could be dried *in vacuo* to a powder, $[\alpha]_D^{25} -16^\circ$ (*c*, 1 in chloroform), the elemental analysis of which suggested high purity. The n.m.r. spectrum of 33 is reproduced in Fig. 15 and the parameters are presented in Table 17.

Anal. Calcd. for $C_{17}H_{22}N_2O_9$: C, 51.25; H, 5.57; N, 7.03%.

Found: C, 50.97; H, 5.36; N, 7.05%.

13. 3-Methyl-1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazolium Iodide (47)

1-(Tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32), 398 mg (1 mmole), was dissolved in dry acetonitrile, 2 ml, and an excess of methyl iodide, 1 ml, was added. The solution was refluxed on a steam bath for 2 h. The solvents were removed by evaporation under diminished pressure and the residue dried *in vacuo* to a light yellow powder (near quantitative yield). Although this material, $[\alpha]_D^{25} +21^\circ$ (*c*, 1 in chloroform), failed to crystallize, the elemental analysis indicated high purity. The n.m.r. spectrum of 47 is reproduced in Fig. 14 and

the parameters are presented in Table 16.

Anal. Calcd. for $C_{18}H_{25}N_2O_9I$: C, 40.00; H, 4.63; N, 5.18; I, 23.52%. Found: C, 39.94; H, 4.53; N, 5.18; I, 23.78%.

14. 3-Methyl-1-(tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazolium Iodide
(48)

1-(Tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazole (33), 398 mg (1 mmole), was dissolved in anhydrous acetonitrile, 2 ml. To this solution was added methyl iodide, 1 ml, and the mixture was heated on a steam bath for 2 h. The excess of methyl iodide and acetonitrile were removed under diminished pressure and the residue dried *in vacuo*. The product, 540 mg (100%), was crystallized from methanol to yield 48 m.p. 225-227°, $[\alpha]_D^{25} +5^\circ$ (*c*, 1 in chloroform), with the n.m.r. spectrum reproduced in Fig. 16. The n.m.r. parameters are presented in Table 18.

Anal. Calcd. for $C_{18}H_{25}N_2O_9I$: C, 40.00; H, 4.63; N, 5.18%. Found: C, 39.85; H, 4.47; N, 5.19%.

15. 1-(α -D-Mannopyranosyl)-imidazole (53)

1-(Tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32), 1.0 g, was dissolved in a mixture of methanol and water (1:1), 20 ml, and to this solution was added triethylamine, 4.2 ml. The reaction mixture was allowed to stand at room temperature overnight. The solvents were then removed under diminished pressure and the residue dried *in vacuo*. Crystallization from a mixture of ethanol and ethyl acetate afforded 0.5 g (86%) of 53, m.p. 180-82°, $[\alpha]_D^{25} +66^\circ$ (*c*, 1 in water). The n.m.r. spectrum of 53 is reproduced in Fig. 21 and the parameters are presented in Table 21.

Anal. Calcd. for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17%.

Found: C, 47.07; H, 6.35; N, 11.87%.

16. 3-Methyl-1-(α -D-mannopyranosyl)-imidazolium Iodide (54)

1-(α -D-Mannopyranosyl)-imidazole (53), 0.5 g, was suspended in anhydrous acetonitrile, 5 ml, and to this was added methyl iodide, 2 ml. The reaction mixture was heated on the steam bath for 5 h. The solvents were then removed under diminished pressure which gave a residue in quantitative yield. When this residue was dissolved in methanol and set aside in the refrigerator, it afforded crystals, m.p. 155-57°, $[\alpha]_D^{25} +46^\circ$ (c, 1 in water). The n.m.r. spectrum of 54 is reproduced in Fig. 22 and the parameters are presented in Table 22.

Anal. Calcd. for $C_{10}H_{17}N_2O_5I$: C, 32.25; H, 4.57; N, 7.52; I, 34.14%. Found: C, 32.22; H, 4.46; N, 7.87; I, 34.43%.

17. 1-(β -D-Mannopyranosyl)-imidazole (55)

1-(Tetra-O-acetyl- β -D-mannopyranosyl)-imidazole (33), 1.5 g, was dissolved in a mixture of methanol and water (1:1), 30 ml, and to this solution was added triethylamine, 6.3 ml. The reaction mixture was kept overnight at room temperature, and then concentrated under diminished pressure. The residue was dried *in vacuo* and crystallization from ethanol gave 0.75 g (90%), 55, m.p. 243-245°, $[\alpha]_D^{25} +27^\circ$ (c, 1 in water). The n.m.r. spectrum is reproduced in Fig. 23.

N.m.r. data: τ 3.94 (1 proton, doublet, $H_{1'}$, $J_{1',2'}$ 1.3 Hz) and 5.45 (1 proton, quartet, $H_{2'}$, $J_{2',3'}$ 2.7 Hz).

Anal. Calcd. for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17%.

Found: C, 46.76; H, 5.97; N, 12.20%.

18. 3-Methyl-1-(β -D-mannopyranosyl)-imidazolium Iodide (56)

1-(β -D-Mannopyranosyl)-imidazole (55), 0.5 g, was suspended in anhydrous acetonitrile, 5 ml, and to this was added methyl iodide, 2 ml. The mixture was refluxed on the steam bath for 5 h. The solvents were then evaporated under diminished pressure and the residue dried *in vacuo* (0.8 g, 100%). Crystallization from methanol afforded 56, m.p. 148-49°, $[\alpha]_D^{25} +17^\circ$ (c, 1 in water). The n.m.r. spectrum of 56 is shown in Fig. 24.

N.m.r. data: τ 3.59 (1 proton, doublet, $H_{1'}$, $J_{1',2'}$ 1.2 Hz); 5.22 (1 proton, quartet, $H_{2'}$, $J_{2',3'}$ 2.8 Hz), and 5.59 (3 protons, singlet N-CH₃).

Anal. Calcd. for C₁₀H₁₇N₂O₅I: C, 32.25, H, 4.57; N, 7.52%. Found C, 32.37; H, 4.53; N, 7.27%.

19. Tri-O-acetyl-1',2'-O-(1-*exo* and *endo*-N-imidazolyl ethylidene)- β -D-mannopyranoses (34 and 35)

(i) Tetra-O-acetyl- α -D-mannopyranosyl bromide (25), 1.027 g (2.5 mmoles), and imidazole, 0.34 g (5 mmoles), were dissolved in anhydrous acetonitrile, 5 ml. The reaction mixture was allowed to stand at room temperature and after 9 h, all the tetra-O-acetyl- α -D-mannopyranosyl bromide (25) had reacted as was indicated by t.l.c. After a work-up similar to that previously described, a residue was obtained which showed only one spot on t.l.c. However, the n.m.r. spectrum showed the presence of two components, one (34) with signals at τ 4.49 (1 proton, doublet, $H_{1'}$, $J_{1',2'}$ 2.6 Hz) and 5.66 (1 proton, triplet, $H_{2'}$, $J_{2',3'}$ 3.5 Hz) and the other (35) with signals at τ 4.53 (1 proton, doublet, $H_{1'}$, $J_{1',2'}$ 2.3 Hz) and 5.48 (1 proton, triplet, $H_{2'}$, $J_{2',3'}$ 3.5 Hz).

The compounds were evidently the diastereoisomeric orthoamides and integration of the signals for the anomeric protons (at τ 4.49 and 4.53) showed that these were formed in a 2:1 ratio, respectively. The *exo*-configuration is *provisionally* assigned to 34 on the basis that it is formed more rapidly than 35. However, as will be seen below these compounds differ little in stability.

(ii) Tetra-*O*-acetyl- α -D-mannopyranosyl bromide (25), 1.027 g (2.5 mmoles), imidazole, 0.34 g (5 mmoles), and triethylamine, 0.35 ml (2.5 mmoles), were dissolved in anhydrous acetonitrile, 5 ml. The reaction mixture was allowed to stand at room temperature for 16 h. The n.m.r. spectrum (Fig. 5) was determined on the residue resulting from a normal work-up, the integrated signals for the anomeric protons (at τ 4.49 and 4.53) showed that the orthoamides 34 and 35 were formed in a 1:1 ratio.

20. 1-(Tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32) and 1-(Tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazole (33) from Tri-*O*-acetyl-1',2'-*O*-(1-*exo*- and *endo*-*N*-imidazolyl ethylidene)- β -D-mannopyranoses (34 and 35)

(i) The 2:1 mixture of the orthoamides 34 and 35, 0.398 g [1 mmole; Expt. II C, 19 (i)], and imidazole hydrobromide, 0.148 g (1 mmole), were dissolved in anhydrous acetonitrile, 5 ml. The reaction mixture was heated under reflux for 4 h. After a work-up similar to that previously described, a residue was obtained, the n.m.r. spectrum of which showed the presence of α -*N*-mannoside 32 and β -*N*-mannoside 33 in 3:2 ratio, respectively.

(ii) The 1:1 mixture of the orthoamides 34 and 35, 0.398 g [1 mmole, Expt. II C, 19 (ii)], and imidazole hydrobromide, 0.148 g (1 mmole), were dissolved in anhydrous acetonitrile, 5 ml, and the reaction mixture

heated under reflux for 4 h. Normal work-up of the reaction mixture furnished a syrupy residue, the n.m.r. spectrum of which showed the presence of α -*N*-mannoside 32 and β -*N*-mannoside 33 in 3:2 ratio, respectively.

21. A Study of the Reactions of Tetra-*O*-acetyl- α -D-mannopyranosyl Bromide (25) with Imidazole

(i) Tetra-*O*-acetyl- α -D-mannopyranosyl bromide (25), 1.027 g (2.5 mmoles), tetra-*n*-butylammonium bromide, 0.805 g (2.5 mmoles), and imidazole, 0.34 g (5 mmoles), were dissolved in anhydrous acetonitrile, 5 ml. The reaction mixture was heated under reflux for 4 h, after which it was worked up in the usual manner. The n.m.r. spectrum of the residue thus obtained showed it to consist of 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32, 30%), 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (33, 20%) and the tetraacetates 29 and 31 (7% combined yield).

(ii) Tetra-*O*-acetyl- α -D-mannopyranosyl bromide (25), 1.027 g (2.5 mmoles), tetra-*n*-butylammonium bromide, 0.805 g (2.5 mmoles), triethylamine, 0.35 ml (2.5 mmoles), and imidazole, 0.34 g (5 mmoles) were dissolved in anhydrous acetonitrile, 5 ml. After 6 h all the starting material, (25) had reacted (t.l.c.). Following the usual procedure for isolation of the product, a sirupy residue was obtained which was dried *in vacuo*. The n.m.r. spectrum showed it to consist of the orthoamides 34 and 35 in a 2:1 ratio, respectively.

(iii) The experiment was repeated as in 21 (ii) except that the reaction mixture was allowed to stand at room temperature for 16 h. The product was isolated following the usual procedure, the n.m.r. spectrum

of which showed it to consist of equal amounts of the orthoamides 34 and 35.

(iv) The experiment was repeated as in 21 (ii) except that the reaction mixture was allowed to stand at room temperature for 7 days. Following the usual procedure for isolation of the product, a residue was obtained, the n.m.r. spectrum of which showed it to consist of about equal amounts of the orthoamides 34 and 35.

(v) Tetra-*O*-acetyl- α -D-mannopyranosyl bromide (25), 1.027 g (2.5 mmoles), tetra-*n*-butylammonium bromide, 0.805 g (2.5 mmoles), and imidazole, 0.34 g (5 mmoles), were dissolved in anhydrous acetonitrile, 5 ml. This mixture was allowed to stand at room temperature for 12 h, after which the product was isolated in the usual manner. The n.m.r. spectrum of the residue thus obtained showed the presence of the orthoamides 34 and 35 in a 2:1 ratio, respectively.

(vi) The experiment was repeated as in 21 (v) except that the reaction mixture was allowed to stand at room temperature for 40 h. Following the usual procedure for the isolation of the product, a residue was obtained, the n.m.r. spectrum of which showed the presence of the orthoamides 34 and 35 in 2:1 ratio, respectively. There was some evidence for the presence of α - and β -*N*-mannosides 32 and 33 in amounts of $\sim 5\%$.

(vii) Tetra-*O*-acetyl- α -D-mannopyranosyl bromide (25), 1.027 g (2.5 mmoles), and imidazole, 0.34 g (5 mmoles), were dissolved in anhydrous acetonitrile, 5 ml, and the reaction mixture allowed to stand at room temperature for 10 h. The product was isolated in the usual manner and its n.m.r. spectrum showed it to consist of the orthoamides 34 and 35 in 2:1 ratio, respectively.

(viii) The experiment was repeated as in 21 (vii) except that the mixture was heated under reflux for 4 h. The n.m.r. spectrum, determined on the residue obtained in the usual manner, revealed the presence of α - and β -*N*-mannosides 32 and 33 in 3:2 ratio, respectively.

22. Tri-*O*-acetyl- $\underline{\underline{D}}$ -ribofuranosyl Bromides (37 and 38)

Although the preparation of this compound has been described in the literature (83), the following procedure which involved a lesser number of steps was adopted. In this study the bromides 37 and 38 were prepared from tetra-*O*-acetyl- β - $\underline{\underline{D}}$ -ribofuranose (36) (84), following the method employed by Stevens and Fletcher (85) for the preparation of the analogous tri-*O*-benzoyl derivative. Anhydrous hydrogen bromide was bubbled into an ice-cold solution of tetra-*O*-acetyl- β - $\underline{\underline{D}}$ -ribofuranose, 9.54 g (30 mmoles), in dichloromethane, 100 ml, for 15 min. After keeping the solution at 0°C for 1 h and then at room temperature for 15 min, it was evaporated under diminished pressure to a thin syrup. Dry dichloromethane and dry toluene were added successively and removed by distillation *in vacuo* to a thin syrup, which was used immediately for condensation reactions. The n.m.r. spectrum of the syrup, reproduced in Fig 1, exhibited a singlet at τ 3.67 (H_1 of the β - $\underline{\underline{D}}$ -anomer 37) and a doublet at τ 3.26 (H_1 of the α - $\underline{\underline{D}}$ -anomer 38, $J_{1,2}$ 4.2 Hz). By the method of integration, the ratio of the α - and β -anomers was about one. The unreacted starting material 36, τ 3.84 (H_1 , singlet) was present in the order of 5%.

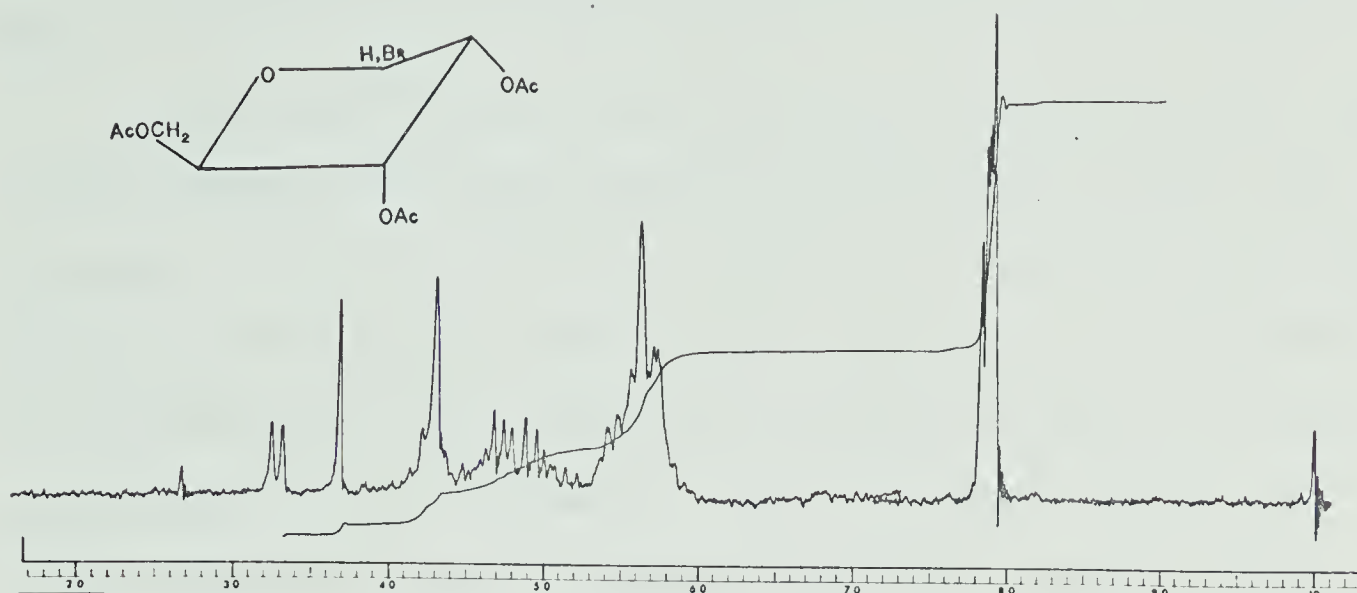


Fig. 1. N.m.r. spectrum (60 MHz) of the anomeric mixture of tri-*O*-acetyl- $\underline{\underline{D}}$ -ribofuranosyl bromides (37 and 38) in deuteriochloroform.^a

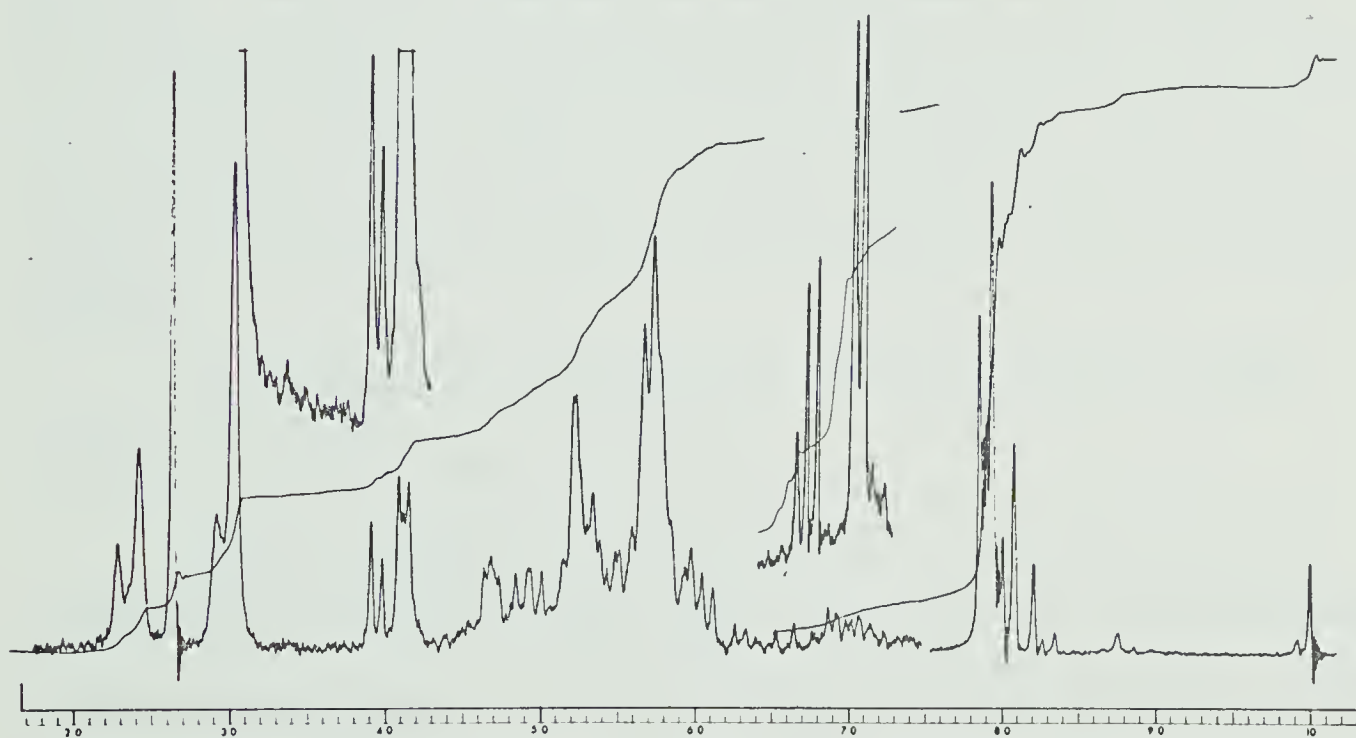


Fig. 2. N.m.r. spectrum (60 MHz) of the product of the reaction of a mixture of tri-*O*-acetyl- $\underline{\underline{D}}$ -ribofuranosyl bromides and imidazole in deuteriochloroform. Inset 100 MHz. [Experimental 30 (iii)].

^aThe conformational drawings of structural formulas drawn on the n.m.r. spectra for some molecules do not represent the true conformation.

23. 1-(Tri-*O*-acetyl- α -D-ribofuranosyl)-imidazole (39) and the β -Anomer (40)

The sirupy mixture of tri-*O*-acetyl-D-ribofuranosyl bromides (37 and 38) prepared from tetra-*O*-acetyl- β -D-ribofuranose (9.54 g), and imidazole, 4.0 g, were dissolved in anhydrous acetonitrile, 40 ml. The mixture was heated under reflux on a steam bath for 3 h. The product was isolated in the usual manner and its examination by t.l.c. showed the presence of three components. Since all attempts to obtain any single component in pure crystalline state always gave crystalline mixture of two components, the residue was subjected to column chromatography (column diameter, 3 cm and silicic acid, 400 g).

The first fraction collected was tetra-*O*-acetyl- β -D-ribofuranose (36, 5%). The second fraction was 1-(tri-*O*-acetyl- β -D-ribofurano-syl)-imidazole 40, 45% recovered yield. Crystallization from ethanol gave 40, m.p. 94-96°, $[\alpha]_D^{25} -22^\circ$ (*c*, 1 in chloroform). The n.m.r. spectrum is reproduced in Fig. 27 and the parameters are presented in Table 26.

Anal. Calcd. for $C_{14}H_{18}N_2O_7$: C, 51.53; H, 5.52; N, 8.58%.

Found: C, 51.90; H, 5.81; N, 8.63%.

The last fraction from the column was 1-(tri-*O*-acetyl- α -D-ribofuranosyl)-imidazole (39), $[\alpha]_D^{25} \approx +103^\circ$ (*c*, ~ 1.7 in chloroform), in 4% recovered yield. It could not be induced to crystallize. The n.m.r. spectrum is reproduced in Fig. 32 and the parameters are presented in Table 31.

24. 3-Methyl-1-(tri-*O*-acetyl- α -D-ribofuranosyl)-imidazolium Iodide (63)

1-(Tri-*O*-acetyl- α -D-ribofuranosyl)-imidazole (39), 50 mg, was dissolved in anhydrous acetonitrile, 2 ml, and an excess of methyl iodide, 1 ml, was added. The solution was refluxed on a steam bath for 2 h. The solvents were then removed by evaporation under diminished pressure and the residue dried *in vacuo* to a pale yellow syrup, 72 mg ($\sim 100\%$), $[\alpha]_D^{25} \sim +44^\circ$ (c , ~ 0.7 in chloroform), which failed to crystallize. The n.m.r. spectrum of the product is reproduced in Fig. 33 and the parameters are presented in Table 32.

25. 3-Methyl-1-(tri-*O*-acetyl- β -D-ribofuranosyl)-imidazolium Iodide (59)

1-(Tri-*O*-acetyl- β -D-ribofuranosyl)-imidazole (40), 105 mg, was dissolved in anhydrous acetonitrile, 5 ml, and an excess of methyl iodide, 1 ml, added. The mixture was refluxed on a steam bath for 2 h. The solvents were then removed by evaporation under diminished pressure and the residue dried *in vacuo* to a pale yellow syrup, 151 mg ($\sim 100\%$), $[\alpha]_D^{25} \approx +2^\circ$ (c , ~ 2 in chloroform). The compound failed to crystallize. The n.m.r. spectrum is reproduced in Fig. 28 and the parameters are presented in Table 27.

26. 1-(α -D-Ribofuranosyl)-imidazole (64)

1-(Tri-*O*-acetyl- α -D-ribofuranosyl)-imidazole (39), 74 mg, was dissolved in a mixture of methanol and water (1:1), 5 ml. To this solution was added triethylamine, 0.5 ml, and the solution allowed to stand overnight at room temperature. The solvents were then removed under diminished pressure and the residue was dried *in vacuo*. The syrup, $[\alpha]_D^{25} \sim +39^\circ$ (c , ~ 0.9 in water), so obtained in 80% yield failed to

crystallize. The n.m.r. spectrum is reproduced in Fig. 34.

N.m.r. data: τ 3.50 (1 proton, doublet, $H_{1'}$, $J_{1',2'}$ 4.3 Hz).

27. 3-Methyl-1-(α -D-ribofuranosyl)-imidazolium Iodide (65)

1-(α -D-Ribofuranosyl)-imidazole (64), 32 mg, was mixed with anhydrous acetonitrile, 2 ml, and methyl iodide, 1 ml. The mixture was refluxed on the steam bath for 5 h, after which the solvents were removed by evaporation under diminished pressure. This gave in quantitative yield a residue, $[\alpha]_D^{25} \approx +36^\circ$ (c , ~ 1.5 in water), which failed to crystallize but was characterized as compound 65. The n.m.r. spectrum is reproduced in Fig. 35.

N.m.r. data: τ 3.38 (1 proton, doublet, $H_{1'}$, $J_{1',2'}$ 4.8 Hz) and 5.67 (3 protons, singlet, N-CH₃).

28. 1-(β -D-Ribofuranosyl)-imidazole (57)

1-(Tri-O-acetyl- β -D-ribofuranosyl)-imidazole (40), 2.0 g, was dissolved in a mixture of methanol and water (1:1); 40 ml. To this solution was added triethylamine, 6 ml, and the solution was allowed to stand overnight at room temperature. The solvents were then removed under diminished pressure and the residue dried *in vacuo*. The residue when dissolved in methanol gave 1.1 g (89%) of 57, m.p. 198-200°, $[\alpha]_D^{25} -131^\circ$ (c , 2 in water). The 220 MHz n.m.r. spectrum is reproduced in Fig. 25 and the parameters are presented in Table 23.

Anal. Calcd. for C₈H₁₂N₂O₄: C, 48.00; H, 6.00; N, 14.00%.

Found: C, 47.78; H, 6.16; N, 13.75%.

29. 3-Methyl-1-(β - $\underline{\underline{D}}$ -ribofuranosyl)-imidazolium Iodide (58)

1-(β - $\underline{\underline{D}}$ -Ribofuranosyl)-imidazole (57), 0.2 g, was suspended in anhydrous acetonitrile, 5 ml, and to this was added methyl iodide, 1 ml. The mixture was refluxed on the steam bath for 5 h. The solvents were then removed under diminished pressure and the residue dried *in vacuo*. This product, 340 mg (100%), $[\alpha]_D^{25} \approx -24^\circ$ (*c*, ~ 1.6 in water), although could not be induced to crystallize was characterized as compound 58. The n.m.r. spectrum is reproduced in Fig. 26 and the parameters are presented in Table 24.

30. A Study of the Reactions of Tri-*O*-acetyl- $\underline{\underline{D}}$ -ribofuranosyl Bromide with Imidazole.

Tri-*O*-acetyl- $\underline{\underline{D}}$ -ribofuranosyl bromide was prepared from 9.54 g (30 mmoles) of tetra-*O*-acetyl- β - $\underline{\underline{D}}$ -ribofuranose in the manner described above (p. 47). The total syrup was divided in five equal parts. The n.m.r. spectrum of a portion of the first part revealed it to consist of α - and β -anomers 38 and 37, in nearly equal quantities. Tetra-*O*-acetyl- β - $\underline{\underline{D}}$ -ribofuranose was also present to an extent of 5%. The other four portions were used for the following experiments.

(i) A mixture of tri-*O*-acetyl- $\underline{\underline{D}}$ -ribofuranosyl bromides, ~ 2.0 g (~ 6 mmoles), and imidazole, 0.8 g (12 mmoles), were dissolved in anhydrous acetonitrile, 5 ml, at 0°C . The mixture was allowed to stand at 0°C for 30 min, after which the product was isolated in the usual manner. The n.m.r. spectrum of the residue showed it to consist of the orthoamide 42 and the β -*N*-riboside 40 in 1:3 ratio, respectively. The unreacted tetraacetate 36, originally present in the starting material, was present to an extent of 8%.

- (ii) The reaction was repeated as in 30 (i) except that the reaction time was 4 h at 0°C. Following the usual procedure for the isolation of the product, a sirupy residue was obtained, the n.m.r. spectrum of which showed it to consist of the orthoamide 42 and the β -*N*-ribose 40 in a 1:3 ratio, respectively. Unreacted 36 was present in the order of 8%.
- (iii) The reaction was repeated as in 30 (i) except that the reaction time was 4 h at room temperature. The product was isolated in the usual manner, the n.m.r. spectrum of which showed it to consist of the orthoamide 42 and the β -*N*-ribose 40 in a 1:4 ratio, respectively. At τ 3.80, a doublet with a spacing of 5.5 Hz indicated the presence of α -*N*-ribose 39 (4%). Unreacted 36 was present in the order of 8% (Fig.2)
- (iv) The reaction was repeated as in 30 (i) but heated under reflux for 3 h. The product was isolated in the usual manner and its n.m.r. spectrum showed the presence of 1-(tri-*O*-acetyl- α -D-ribofuranosyl)-imidazole (39), 1-(tri-*O*-acetyl- β -D-ribofuranosyl)-imidazole (40) and the unreacted tetraacetate 36 in 6:82:12 ratio, respectively.

31. 7-Methyl guanosine (61)

7-Methyl guanosine (61) was prepared from guanosine (60) according to the method of Jones and Robins (86). The compound discolored at 150° and then decomposed about 180°, $[\alpha]_D^{25}$ -9° (*c*, 1.1 in water). The n.m.r. spectrum is reproduced in Fig. 30 and the parameters are presented in Table 28.

Anal. Calcd. for $C_{11}H_{15}N_5O_5 \cdot 2H_2O$: C, 39.60; H, 5.70%. Found: C, 39.56; H, 4.51%

32. 1,7-Dimethyl guanosine Iodide (62)

The title compound was prepared according to the method of Zoltewicz and coworkers (87). The compound discolored at 150° $[\alpha]_D^{25} -3^\circ$ (*c*, 1 in water). The n.m.r. spectrum is reproduced in Fig. 31 and the parameters are presented in Table 28.

Anal. Calcd. for $C_{12}H_{18}N_5O_5I$: C, 32.80; H, 4.10; N, 15.90%.

Found: C, 32.60; H, 4.13; N, 15.53%.

III RESULTS AND DISCUSSION

A. Synthesis and Mechanism of Formation of *N*-Glycosyl Imidazoles

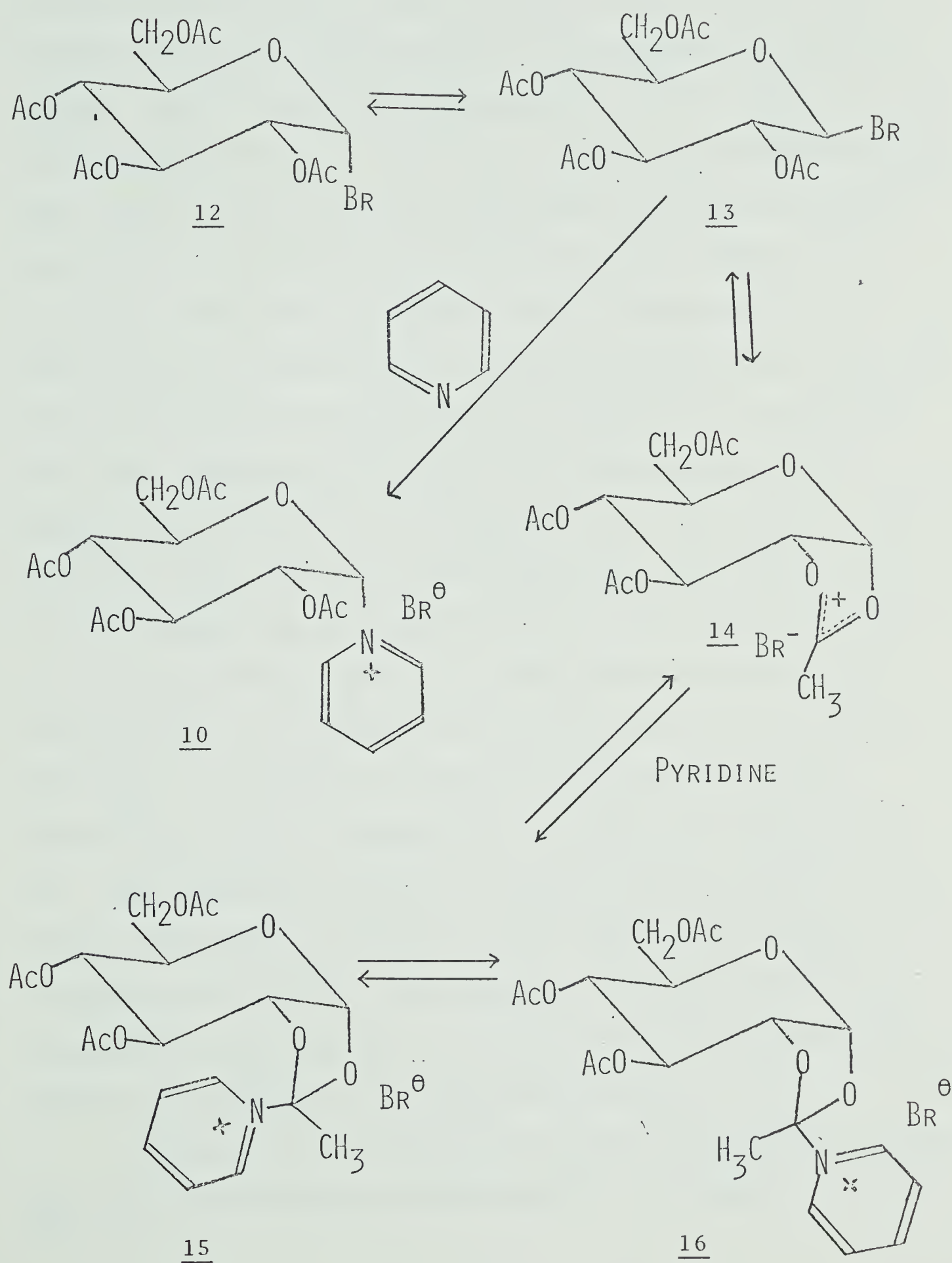
The main objective of the present investigation was to obtain, by synthetic means, *N*-glycosides of imidazole possessing the α -configuration and study their conformational properties.

Crystalline 1-(tetra-*O*-acetyl- $\underline{\underline{D}}$ -glucopyranosyl)-imidazole was prepared in 1936 by Bergman and Heimhold (82) by the heavy metal salt condensation method but the configuration at the anomeric carbon atom was not established. It is well known that the condensation of the heavy metal salts of imidazoles and related bases with suitably *O*-protected 1,2-*cis*-glycosyl halides, in general, give the 1,2-*trans*-*N*-glycosides (88). In order to establish unequivocally the anomeric configuration of the above compound by means of n.m.r. spectroscopy (5,89), the preparation of Bergman and Heimhold (82) was repeated. A crystalline compound was readily obtained with a melting point, 217°, in close agreement with the reported value. Since the n.m.r. spectrum of the compound (Fig. 9) showed only a singlet at τ 4.72 for the four methine protons of the glucopyranose ring, it was not possible to make an assignment of configuration at the anomeric center. The *O*-deacetylated product, m.p. 227-228° [reported (82) 217°], however, possessed a n.m.r. spectrum which showed a doublet at τ 4.25 with a spacing of 8.5 Hz for the anomeric proton. A coupling constant of this magnitude for H_1' corresponds to a torsional angle of about 180° for $H_1-C_1-C_2-H_2$, which requires the *N*-glucoside to possess the β -configuration (5). In order to synthesize the α -*N*-glucosides required in this research, an alternative

route was therefore required.

In 1965, Lemieux and Morgan (90) reported that when tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), was reacted with pyridine, a 3:2 mixture of the anomeric *N*-(tetra-*O*-acetyl-D-glucopyranosyl)-pyridinium bromides was formed in which the α -anomer predominated. When the same reaction was carried out in the presence of tetra-*n*-butylammonium bromide, the product was the α -anomer formed in more than 90% yield. These authors concluded that the initial presence of the bromide ion in the reaction mixture led to a rapid equilibration of the starting material, α -bromide 12, with its β -anomer 13 and that the thermodynamically less stable β -bromide was the source of the *N*-(tetra-*O*-acetyl- α -D-glucopyranosyl)-pyridinium bromide (10). Although, the mechanism by which the β -bromide 13 was converted to 10 was not known in detail, the authors did not rule out the possibility that the α -pyridinium glucoside 10 could be formed by way of the intermediate acetoxonium ion. As illustrated (Diag. 1) this ion 14, in the presence of pyridine can be in equilibrium with the orthoamide type intermediates 15 and 16. Rearrangement of the *endo*-orthoamide 15 would then lead to 10. However, support for this contention could not be obtained and it is possible that the formation of the acetoxonium ion intermediate is merely an abortive reaction, in that this ion returns to the β -bromide (77), which is the actual precursor of the α -pyridinium glucoside 10. That is the α -*N*-glucoside 10 may arise from nucleophilic attack of pyridine on the β -bromide in competition with its solvolysis to the acetoxonium ion. This proposed mechanism of formation of the α -*N*-glucopyranosyl pyridinium bromides by halide-ion catalysis appeared attractive for the syntheses of the

Diagram 1

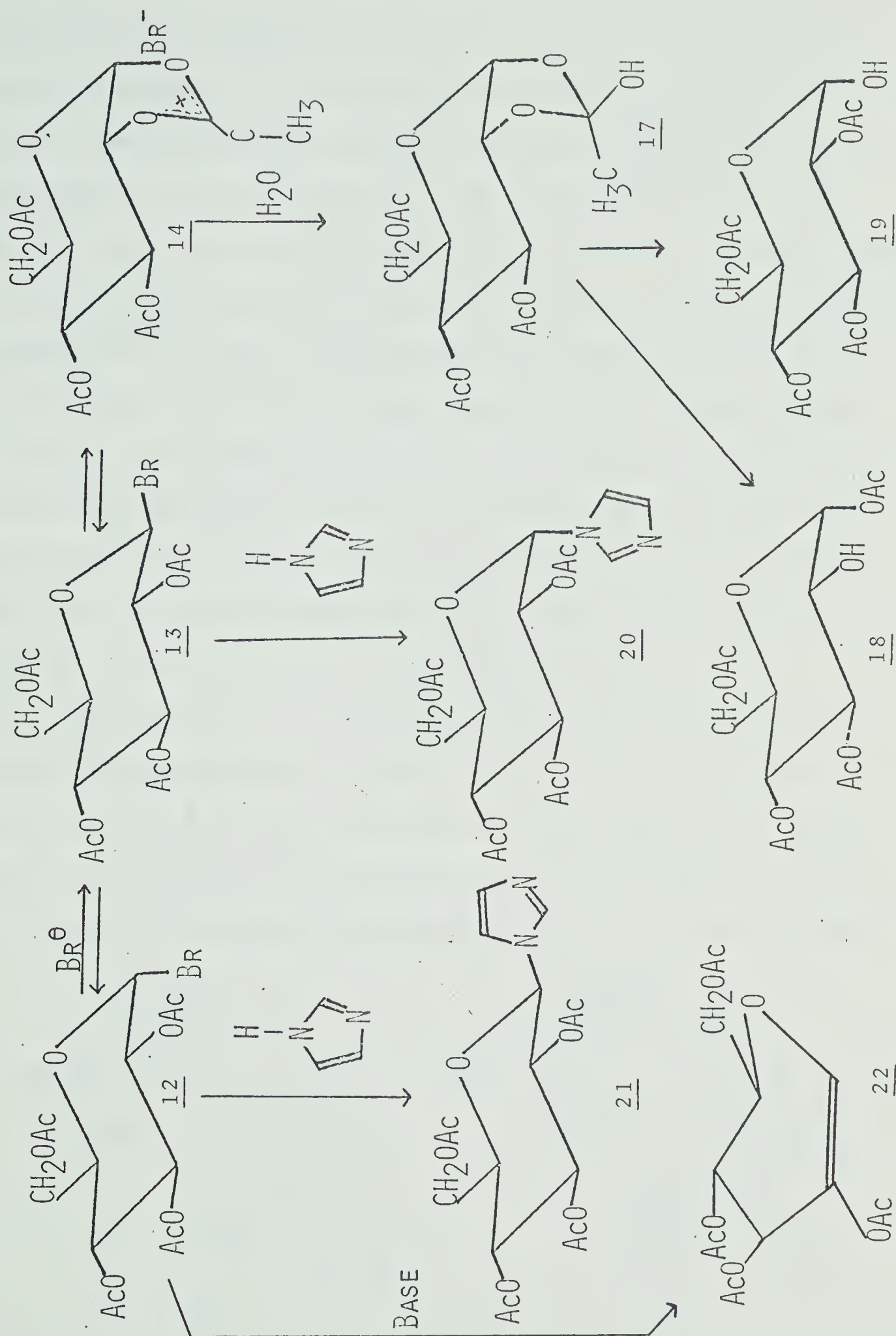


α -*N*-glucopyranosyl imidazoles required in this study.

When tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), imidazole and tetra-*n*-butylammonium bromide were heated under reflux in acetonitrile for 4 h, both 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20) and 1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21) were formed as major products. 1,3,4,6-Tetra-*O*-acetyl- α -D-glucopyranose (18) (80), 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose (19) (80) and tetra-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enopyranose (22) were formed as by-products. These were separated by column chromatography. The identity of the 1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21) was readily established by direct comparison of its n.m.r. spectrum with that of the compound made according to the method of Bergman and Heimhold (82), for which the β -configuration was established as shown above. The n.m.r. spectrum of the α -anomer 20 is reproduced in Fig. 6 and the parameters are presented in Table 9. The coupling constants for the pyranose ring protons are in good agreement with the α -*gluco*-configuration and its conformation will be discussed in detail later. Furthermore, the high *dextro* rotation, $+111^\circ$, observed for 20 as compared to -9° for the β -anomer 21 is in accord with this assignment (2). Also, the chemical shift of the anomeric proton of 20 is at lower field (τ 3.90) than that of 21 (τ 4.72) as expected (5) from this configurational assignment. The structures of 18, 19 and 22 were established by comparing their n.m.r. spectra with those of authentic samples as is discussed in the Experimental Section.

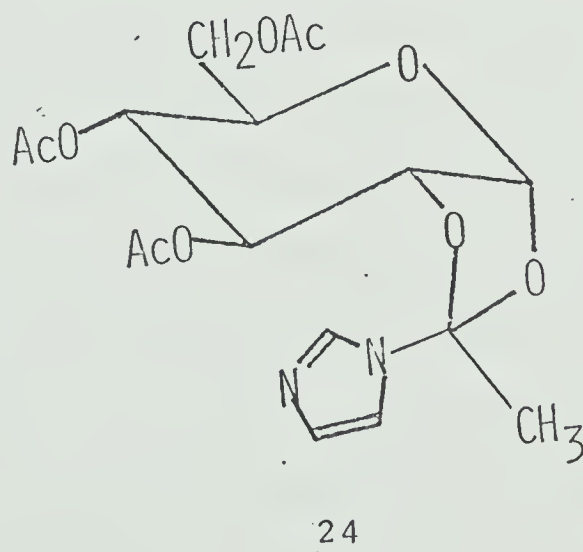
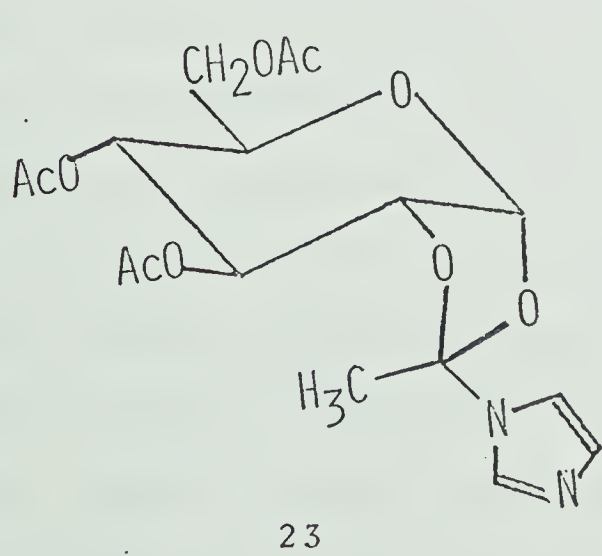
The formation of 1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21) can be rationalized, at first thought, as a nucleophilic attack of

Diagram 2



imidazole on the α -bromide 12 causing an inversion of configuration at the anomeric center. It is well known that in the presence of added bromide, a rapid equilibrium between the anomeric halides 12 and 13 is established as depicted in Diagram 2 (77). Nucleophilic attack of imidazole on the intermediate β -bromide 13 thus produced can furnish the α -anomer 18. The mechanism of formation of 20 and 21 will be discussed in greater detail later. The formation of the compounds 18 and 19 can be rationalized in terms of a common precursor, the orthoacid 17 (90). It is known that compound 13 undergoes anchimerically assisted displacement of the bromide ion to yield the 1,2-acetoxonium ion 14, which may react with traces of water, almost inevitably present in the reaction medium (91) to yield the orthoacid 17 (90). Then the rearrangement of 17 to both of the tetraacetates 18 and 19 is possible.

The formation of the acetoxonium ion 14 under the experimental conditions employed is highly probable (77). Since under similar conditions orthoesters have been prepared in high yield (90), a rapid reaction of the ion 14 with imidazole to yield tri-*O*-acetyl-1',2'-*O*-(1-*N*-imidazolyl ethylidene)- α -D-glucopyranoses 23 and 24 would be expected,



provided the liberated hydrogen bromide is captured by a suitable base such as imidazole itself. The compounds of this type (23 and 24) have not been previously isolated; nevertheless the existence of similar structures was postulated by Lemieux and Morgan (90).

Early workers noted that 1,2-orthoesters were formed in reactions under Koenigs-Knorr conditions only with the 1,2-*trans*-acylated glycosyl halides (92). Helferich (93,94), however, discovered that syntheses of 1,2-orthoesters of a sugar were possible starting from an acylated 1,2-*cis*-glycosyl halide. It was shown that the reaction of tetra-*O*-acetyl- α -D-glucopyranosyl bromide with 2-propanol in the presence of *sym*-collidine gave a product which contained over 50% of the 1,2-orthoester. The effect of *sym*-collidine hydrobromide formed during the reaction of isopropanol with the tetra-*O*-acetyl- α -D-glucopyranosyl bromide on the anomerization of the α -bromide to β -bromide which led to the formation of the orthoester, was not recognized by these authors. Lemieux and coworkers (90) reported the generally applicable procedure for the preparation, in high yield, of a 1,2-orthoester involving a reaction of 1,2-*cis*-glucosyl halide with an alcohol in the presence of halide ion and a hindered base. Under these conditions, the formation of the diastereoisomeric 1,2-orthoesters is possible. Both *exo* and *endo* isomers were isolated for the first time by Talley and coworkers (95) in the reaction of tetra-*O*-acetyl- β -D-glucopyranosyl bromide with 1,2,3,4-tetra-*O*-acetyl- β -D-glucopyranose in the presence of silver oxide. In many reactions only one isomer, usually the *exo* one, has been obtained (92). Lemieux and Ciperia (91) suggested that the high degree of stereoselectivity arose because of an easier approach of the alcohol to the side of the acetoxonium ion which is *trans* to the pyranose ring.

In order to examine whether tri-*O*-acetyl-1',2'-*O*-(1-*N*-imidazolethylidene)- α -D-glucopyranoses, 23 and 24, are formed, tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12) was reacted with imidazole in the presence of tetra-*n*-butylammonium bromide and triethylamine at room temperature for 3 h. Under these conditions the orthoamides 23 and 24 were indeed formed. This was apparent from the n.m.r. spectrum (Fig.3) of the reaction mixture which showed two doublets at τ 4.10 and 4.05. These signals must arise from the anomeric protons of the *exo* and *endo* isomers of the orthoamide, respectively, since neither the α -*N*-glucoside 20 nor its β -anomer 21 showed $H_{1'}$ absorptions at these frequencies. When the reaction mixture was reexamined after longer reaction times, the intensity of one of the $H_{1'}$ doublets decreased and at reaction times greater than two days, only one doublet at τ 4.10, consistent with the presence of only one diastereoisomer, was observed. This isomer was isolated in a pure state by the addition of Skelly Solve "C" to a solution of the compound in chloroform. Its n.m.r. spectrum, Fig. 4 in deuteriochloroform gave, as expected, a doublet for $H_{1'}$ at τ 4.25 ($J_{1',2'}$ 5.2 Hz) and the spectrum in general was very similar to that of tri-*O*-acetyl-1,2-*O*-(1'-methoxyethylidene)- α -D-glucopyranose in the region τ 4.2 to 5.3. Furthermore, when the orthoamide 23 was dissolved in warm ethanol, tri-*O*-acetyl-1,2-*O*-(1'-ethoxy ethylidene)- α -D-glucopyranose was readily formed. The structure of the ethyl orthoester was established from elemental analysis and a direct comparison of its n.m.r. spectrum with that of an authentic sample (96).

It is known that tri-*O*-acetyl-1,2-*gluco*-orthoesters which have the *exo*-configuration do not assume the chair conformation, normally observed for the D-glucopyranose derivatives. The pyranose ring is

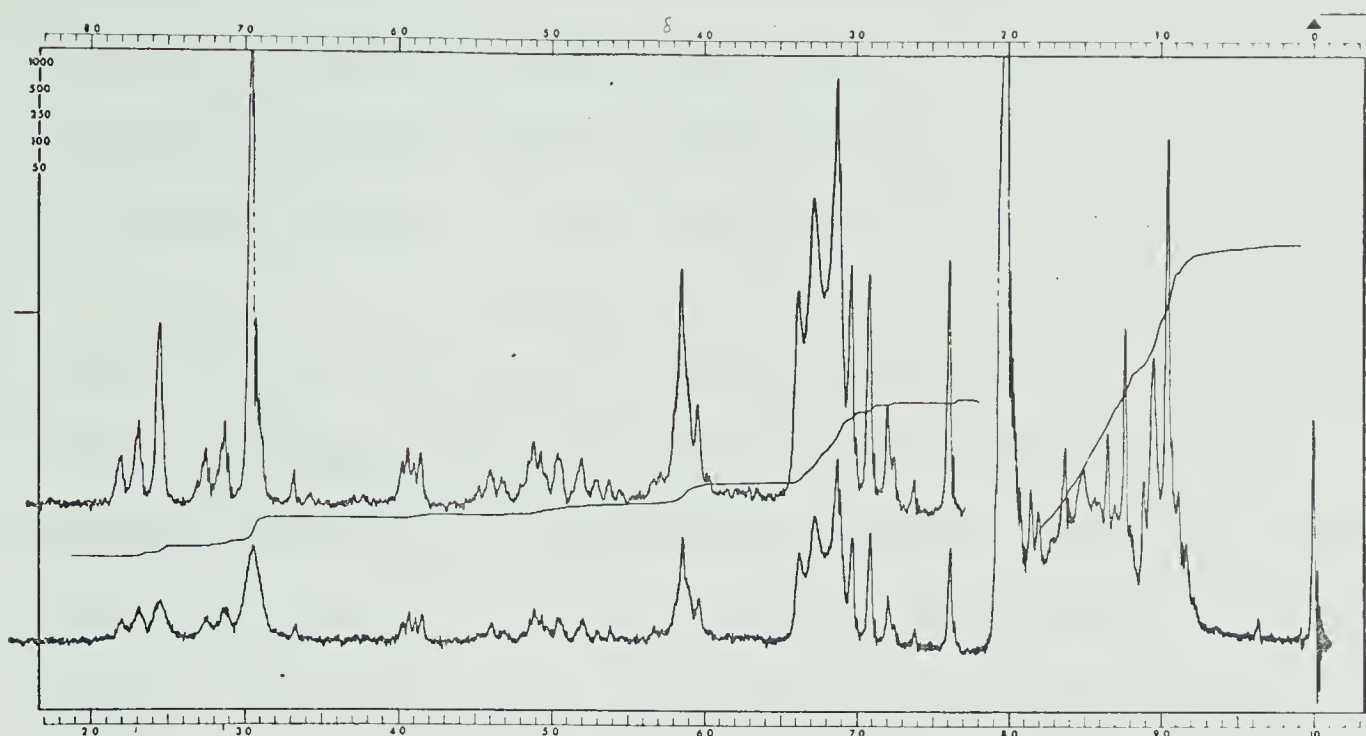


Fig. 3. N.m.r. spectrum (60 MHz) of the reaction of tetra-*O*-acetyl- α -D-glucopyranosyl bromide, imidazole, triethylamine and tetra-*n*-butylammonium bromide in acetonitrile.

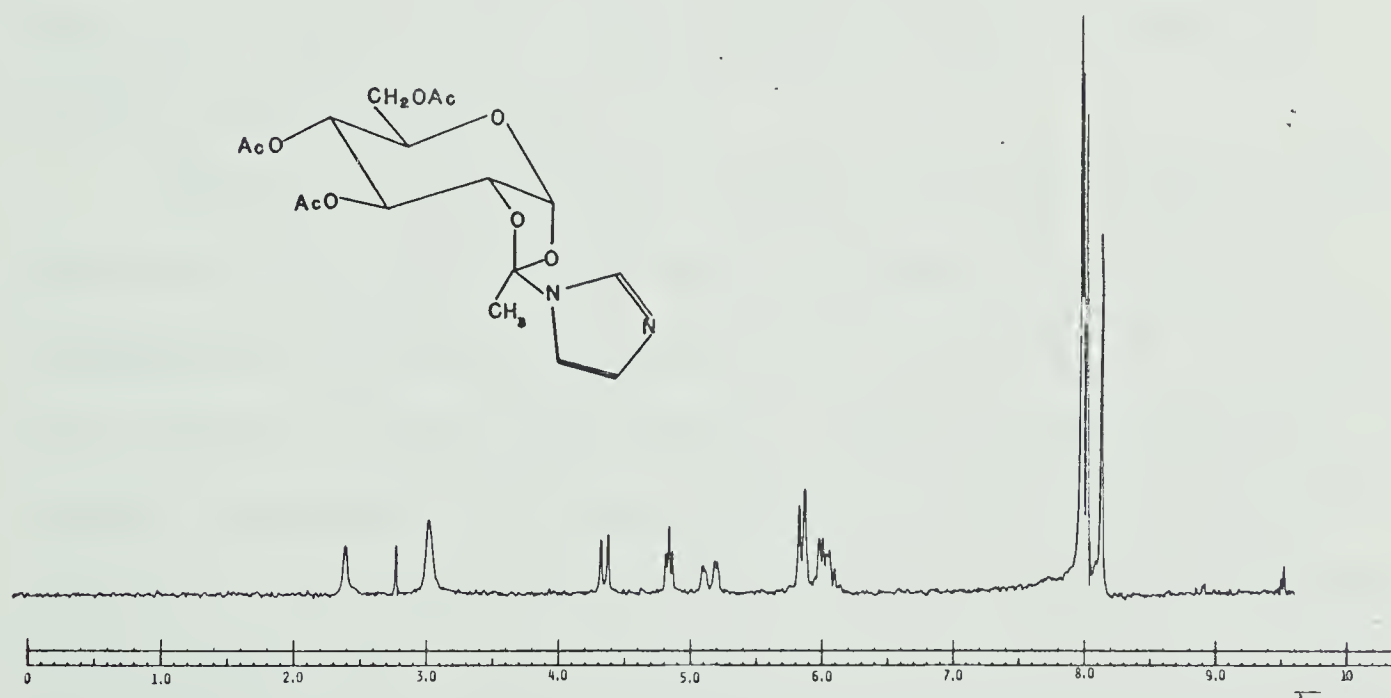


Fig. 4 N.m.r. spectrum (100 MHz) of tri-*O*-acetyl-1',2'-*O*-(1-*exo*-*N*-imidazolyl ethylidene)- α -D-glucopyranose (23) in deuteriochloroform.

slightly distorted (96). A chair conformation would require axial orientation of H_2 , H_3 , H_4 , and H_5 and would be expected to give a n.m.r. spectrum in which the coupling constants are $J_{2,3} \approx J_{3,4} \approx J_{4,5} \sim 9$ Hz. For the same compounds, Lemieux and Morgan (96) observed $J_{2,3} = J_{3,4} = 2.8$, $J_{4,5} = 9$ Hz and calculated that H_3 defines a dihedral angle of about 120° with both H_2 and H_4 while H_4 and H_5 define an angle of about 180° with each other. This indicates that some flattening of the pyranose ring from C_1 to C_3 must have occurred; this is also in agreement with the value of $J_{1,2} = 5.0$ Hz observed for this compound. A coupling constant of this magnitude has also been found for similarly situated bridge-head protons (97), and this suggests a dihedral angle of approximately 40° . In contrast to above, Coxon and Hall (98) proposed a skew-boat conformation for a series of 1,2-*O*-alkylidene derivatives which gave n.m.r. spectra virtually identical to those of the *exo*-alkyl-1,2-orthoesters. These workers suggested dihedral angles of about 42° between H_1 , H_2 ; H_2 , H_3 and H_3 , H_4 .

Using X-ray crystallography, Trotter and Fawcett (99) were able to show that 1,2-*O*-aminoisopropylidene- α -D-glucopyranose hydroiodide (a compound very similar in structure to the discussed 1,2-orthoesters) does not have a skew-boat conformation. Instead, the five-membered dioxolane ring adopts an envelope conformation with C_2 -atom displaced only $0.36 \text{ \AA}$ from the plane of the other four atoms suggesting flattening of the pyranose ring. This was proposed with the full realization that there might be small differences between the conformation of the pyranose ring of a sugar in solution and in the crystalline state. Recently, Lemieux and Detert (100) reached the same conclusion about ring flattening of 1,2-*O*-alkylidene and 1,2-ortholactone derivatives of

3,4,6-tri-*O*-acetyl- α -D-glucopyranose.

The n.m.r. spectrum of the orthoamide 23 isolated in this investigation is reproduced in Fig. 4. The position of H_3' at τ 4.84 was verified by nuclear magnetic double resonance. On irradiation at τ 4.34 (H_1'), the multiplet at $\sim \tau$ 6.0 (H_2') collapsed. Subsequent irradiation of H_2' changed the triplet at τ 4.84 (H_3') into a doublet, also the quartet at τ 5.14 collapsed to a rough doublet, indicating that H_4' is centered at τ 5.14. Subsequent irradiation at τ 5.14 (H_4') changed the triplet at τ 4.84 (H_3') into a doublet with a spacing of 2.3 Hz ($J_{2',3'}$). Irradiation at τ 4.84 (H_3') changed the quartet at τ 5.14 (H_4') to a doublet with a spacing of 9.0 Hz ($J_{4',5'}$). Since $J_{2,3} + J_{3,4} = 5$ Hz, a value of 2.4 Hz was found for $J_{3',4'}$. Using the Karplus relationship (72) and the observed coupling constants, the calculated dihedral angles between the vicinal protons are $\phi_{1',2'} = 40^\circ$, $\phi_{2',3'} = 117^\circ$, $\phi_{3',4'} = 116^\circ$ and $\phi_{4',5'} \approx 180^\circ$. The observed coupling constants $J_{1',2'} = 5.2$; $J_{2',3'} = 2.6$; $J_{3',4'} = 2.4$; $J_{4',5'} = 9$ Hz and the dihedral angles given above are in agreement with the previously discussed flattening of the pyranose ring.

In the case of alkyl-1,2-orthoesters of D-glucose, the observed coupling constants (particularly $J_{2,3}$ and $J_{3,4}$) for the *endo* isomer have been reported to be larger than those for the *exo* isomer (80,100). The orthoamide 23 exhibited coupling constants, particularly $J_{2',3'}$ and $J_{3',4'}$, which were similar in magnitude to those reported for the *exo*-alkyl 1,2-orthoesters and this evidence may be considered sufficient to support the *exo* structure proposed for the orthoamide 23 isolated in this investigation.

In order to investigate the mechanism of the formation of the

N-glucosides 20 and 21, a series of experiments were carried out to determine the effect of the following parameters on the course of the reaction: (i) time of the reaction, (ii) added base (triethylamine), (iii) added bromide (tetra-*n*-butylammonium bromide) and (iv) temperature of the reaction.

Reaction of tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12), imidazole and tetra-*n*-butylammonium bromide in acetonitrile at room temperature for 5 h (Table 7A) gave a product which consisted of the orthoamide 23 (80%) and tetra-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-eno-pyranose (22) (5%) as ascertained from the n.m.r. analysis of the mixture. The remaining 15% consisted of the α - and β -*N*-glucosides 20 and 21; the tetraacetates 18 and 19; unfortunately, the n.m.r. spectrum did not allow an estimation of the ratios of these four compounds.

The effect of added base was next studied initially at room temperature, Table 7B. Thin layer chromatographic monitoring of the reaction showed the gradual disappearance of the starting material 12, which could no longer be detected after 5 h. After this time, the n.m.r. spectrum of the reaction product isolated in the usual manner, showed the presence of the orthoamide 23 (77%) and of 22 (14%). The remaining 9% was a mixture of compounds 18, 19, 20, and 21. When this reaction was repeated, Table 7C, but with heating under reflux, the n.m.r. analysis of the aliquot samples revealed that 20 h elapsed before the orthoamide 23 had reacted completely. The crude product isolated in the usual manner was subjected to chromatographic separation and the following compounds were isolated: α -*N*-glucoside 20 (20%), β -*N*-glucoside 21 (25%) and the tetraacetates 18 and 19 (10%).

TABLE 7

A study of the reaction of tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12) with imidazole^a

Reactions No.	Reactions conditions	Temp.	Time	Yield %						Remarks
				<u>23</u>	<u>20</u>	<u>21</u>	<u>18</u> and <u>19</u>	<u>22</u>		
A	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖] added	25° C	5 h	80	—	—	15	—	5	b
B	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖] and 2.5 mmoles of (C ₂ H ₅) ₃ N added	25° C	5 h	77	—	—	9	—	14	b
C	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖] and 2.5 mmoles of (C ₂ H ₅) ₃ N added	Reflux	20 h	-	20	25	10	-	-	c
D		25° C	5 h	50	-	-	-	-	-	d
E		25° C	12 h	~80	-	-	-	-	<10	b
F	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖] added	Reflux	4 h	-	25	30	7	7-10	-	c

^aAll reactions were carried out with 2.5 mmoles of 12 and 5 mmoles of imidazole in 5 ml of acetonitrile. Other conditions are given below.

^bRepresents ratios as % of compounds in the mixture as determined by n.m.r. spectroscopy.

^cRepresents recovered yields based on the starting material.

^dThe other 50% was unreacted 12.

TABLE 7 (continued)

<u>18</u>	1,3,4,6-Tetra- <i>O</i> -acetyl- α -D-glucopyranose
<u>19</u>	2,3,4,6-Tetra- <i>O</i> -acetyl- α -D-glucopyranose
<u>20</u>	1-(Tetra- <i>O</i> -acetyl- α -D-glucopyranosyl)-imidazole
<u>21</u>	1-(Tetra- <i>O</i> -acetyl- β -D-glucopyranosyl)-imidazole
<u>22</u>	Tetra- <i>O</i> -acetyl-1-deoxy-D- <i>arabino</i> -hex-1-enopyranose
<u>23</u>	Tri- <i>O</i> -acetyl-1,2- <i>O</i> -(1- <i>exo-N</i> -imidazolyl ethylidene)- α -D-glucopyranose

In order to study the effect of added bromide, a standard reaction was carried out with only the starting material 12 and imidazole in acetonitrile at room temperature. After 5 h (Table 7D), a portion of the reaction mixture yielded, following a normal workup procedure, a product which by n.m.r. spectroscopic analysis showed that about 50% of the starting material 12 (H_1 doublet for 12 at τ 3.4, $J_{1,2}$ 3.8 Hz), was still present in the reaction mixture, the rest being the orthoamide 23. After a total of 12 h (Table 7E) all the starting material 12 had essentially reacted (t.l.c.) and the reaction mixture yielded on workup a product consisting mainly of orthoamide 23 ($\sim$ 80%). There was evidence from the n.m.r. spectrum of the product that some of the product of dehydrobromination 22 was formed.

The effect of temperature on the reaction is apparent from the reactions in Table 7. Noteworthy is the reaction (F), which was carried out in (A) but at the refluxing temperature of the solvent for 4 h. In contrast to reaction (A) (room temperature), the orthoamide 23 was not detected, but instead α - and β -*N*-glucosides were formed in 25 and 30% yields, respectively.

It is clear from the above discussion that the orthoamide is the major product of the reaction of tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12) with imidazole in the presence or absence of added bromide at room temperature. The α -bromide 12, first undergoes nucleophilic attack by imidazole with concomitant inversion of the configuration at C_1 , thus releasing bromide ion. The liberated bromide ion then leads to equilibration of the α -bromide (12) with its β -anomer (13). That the bromide ion catalyzes the overall reaction is evident from Table 7A and

7D; the reaction was complete in the presence of added tetra-*n*-butylammonium bromide in 5 h whereas about half the unreacted tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12) was still present after this time in the absence of bromide at the beginning of the reaction. Since the main products of the reaction under mild conditions (Table 7A, 7B, 7D and 7E) are the orthoamides 23 and 24, which can only be formed via the acetoxonium ion 14, it may be concluded that the formation of 14 from 13 is much faster than the formation of the *N*-glucosides. Discussion of the probable mechanisms for the formation of the *N*-glucosides is reserved until after the results of the synthesis of the *manno*- and *ribo* analogs have been described (p. 86).

Lemieux and Hayami (77) have demonstrated that the equilibration of the α - and β -tetra-*O*-acetyl-D-glucopyranosyl chlorides in acetonitrile was first order with respect to chloride ion. The formation of α -*N*-glucoside 20 undoubtedly involves the β -bromide 13 as a precursor. Since virtually the same course was observed for the reaction of α -bromide 12 with imidazole in the presence or in the absence of added tetra-*n*-butylammonium bromide (only the overall rate of reaction was affected), it is apparent that only low levels of bromide ion concentration are required to maintain the α - and β -bromides (12 and 13) in their equilibrium amounts. Lemieux and Hayami (77) demonstrated that tetra-*O*-acetyl- β -D-glucopyranosyl chloride in the presence of one fifth equivalent of tetraethylammonium chloride and with acetonitrile as solvent dissociates to 1,2-acetoxonium ion four times more rapidly than it undergoes anomerization. The equilibrium mixture contains about 94% of the α -anomer. Therefore, it is to be expected

that in the presence of bromide ion, the orthoamides 23 and 24 will rapidly form and accumulate, if their decomposition is a slow process. Indeed, under basic conditions (added triethylamine), these were the initial isolable products of reaction obtained in high yield.

By analogy with the 1,2-orthoesters, the orthoamides would be expected to be acid labile. In agreement with this, it was found that when triethylamine was present in the reaction mixture, heating for 20 h in acetonitrile under reflux was required for the complete disappearance of 23 (Table 7C). On the other hand, when triethylamine was omitted as shown in Table 7F, heating for 4 h was sufficient for its complete disappearance to form essentially the same products.

The formation of tetra-*O*-acetyl-1-deoxy- $\underline{\underline{D}}$ -*arabino*-hex-1-enopyranose (22) may readily be rationalized. Lemieux and Lineback (81) reported that the dehydrobromination of tetra-*O*-acetyl- α - $\underline{\underline{D}}$ -glucopyranosyl bromide (12) to 22 is catalyzed by secondary amines containing *n*-alkyl groups. These workers concluded that catalysis is highly dependent on the structure of the amine used. When the amine used was triethylamine, the compound 22 was formed only in 15% yield, the rest being the *N*-glucosides. These *N*-glucosides were not isolated but their existence inferred from the n.m.r. spectra of the reaction mixture. The intermediate glucosyl-oxo-carbonium ion formed could be converted to products by two different and competing routes. One route would be the formation of a covalent bond (C-N) to form *N*-glucosides. The other route would involve loss of C₂-proton to the amine to give tetra-*O*-acetyl-1-deoxy- $\underline{\underline{D}}$ -*arabino*-hex-1-enopyranose (22). The fact that the amine employed (triethylamine) in the present study is a hindered amine, explains the

formation of *N*-glucosyl imidazoles as the major products. When triethylamine is not used in the reaction mixture (Table 7A), the amount of 22 formed is only 5% as compared to 14% when the amine is used (Table 7B).

The objectives of the present study have already been indicated. Of particular interest was the effect of protonation or *N*-methylation of the imidazole ring on the conformation of the sugar ring moiety. The results of this study will be discussed later. In the case of 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20), however, the coupling constant between H_2' and H_3' could not be determined owing to the complexity of the n.m.r. spectrum, when the sample solution was acidified with trifluoroacetic acid. It was decided, therefore, to synthesize and study the *N*-D-mannopyranosyl imidazoles with the hope that these being epimeric at C_2' with the *N*-glucosides, would be amenable to a complete first order n.m.r. analysis. Furthermore, $J_{1',2'}$ coupling constant for the α -anomer in the mannose series changes considerably going from the 4C_1 to 1C_4 or ${}^{2,5}B$ conformation, since the protons at C_1 and C_2 have equatorial-equatorial or axial-axial relationship, respectively. Thus, the conformational change, if any, on protonation or *N*-methylation of the imidazole moiety in the *manno*-series could be readily observed.

Table 8 summarizes the various parameters employed in the study of the reaction of tetra-*O*-acetyl- α -D-mannopyranosyl bromide (25) with tetra-*n*-butylammonium bromide and imidazole (Table 8A), in refluxing acetonitrile for 4 h, followed by the normal method of isolation of the product and column chromatographic separation yielded 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32, 30%); 1-(tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazole (33, 20%); 1,3,4,6-tetra-*O*-acetyl- β -D-mannopyranose

(29) and 2,3,4,6-tetra-*O*-acetyl- α -D-mannopyranose (31) (combined yield of 29 and 31 *ca.* 7%). Incidentally, the dehydrobromination product, tetra-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enopyranose was not isolated in the present case, whereas it was obtained in yields of 7-10% in the corresponding *gluco*-case. This is understandable if one examines the relationship of the C₂-hydrogen with the α -bromine. The hydrogen atom at C₂ and bromine atom at C₁ are in *trans* diaxial arrangement in the glucosyl bromide thus facilitating the dehydrobromination reaction. On the other hand, the hydrogen atom at C₂ of the mannosyl bromide is *cis*- to the bromine atom and occupies an equatorial orientation.

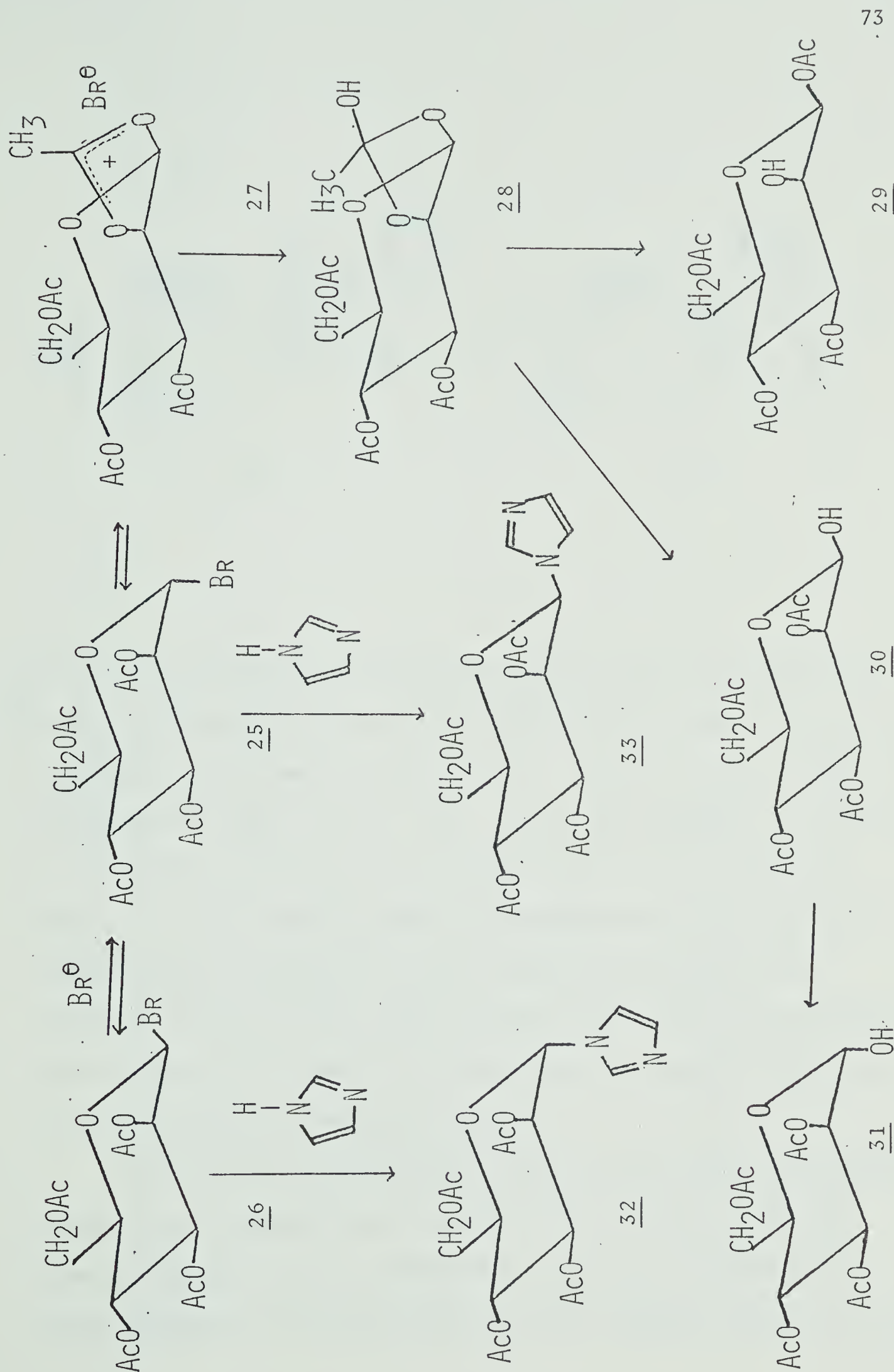
The *N*-mannoside 33 had a specific rotation of -16° in chloroform suggesting the β -configuration at the anomeric center. This was substantiated from the n.m.r. spectrum (Fig. 15), the parameters of which are presented in Table 17. The observed $J_{1',2'}$ was 1 Hz in acetone-*d*₆ and 1.2 Hz in deuteriochloroform. A coupling constant of the magnitude of 1 Hz for the anomeric proton is characteristic of penta-*O*-acetyl- β -D-mannopyranose (64) and this could also be true in the case of 33. The compound 32 had a specific rotation of $\sim +35^\circ$ and was assigned the α -configuration at the anomeric center. This assignment was confirmed from its n.m.r. spectrum (Fig. 12) the parameters (Table 14) of which shall be discussed in greater detail later. The tetra-*O*-acetyl-D-mannopyranoses 29 and 31 were identified by comparing their n.m.r. spectra with those of authentic samples prepared by Lemieux and Detert (80). The anomeric proton of 1,3,4,6-tetra-*O*-acetyl- β -D-mannopyranose (29) appeared at τ 4.20 with a spacing of 1 Hz as expected (64).

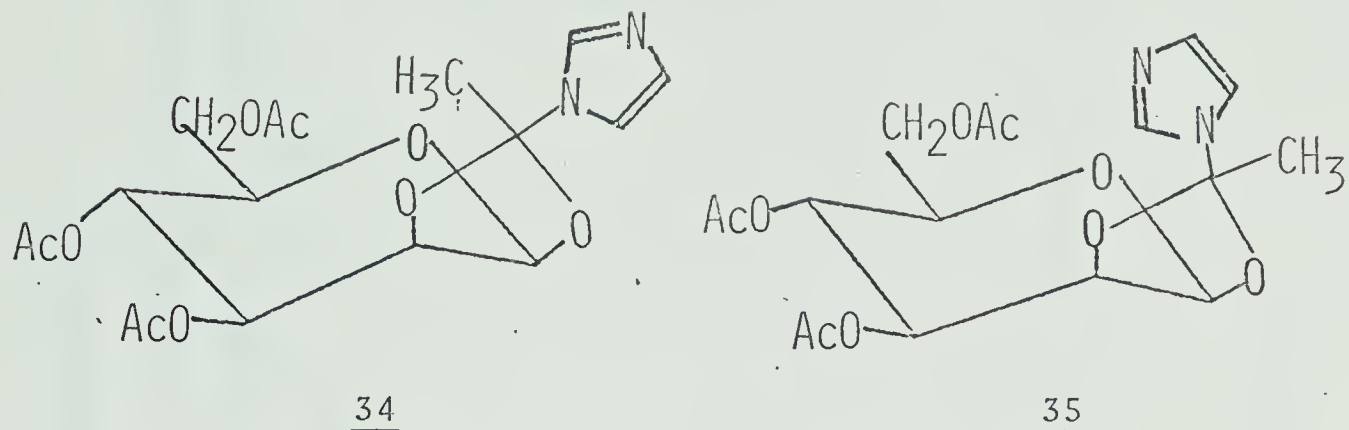
The explanation as to how the above products of this reaction

arise (see Diagram 3) follows a similar line of reasoning to that developed for the D-glucose series. The suggested mechanism for the formation of tetra-*O*-acetates 29 and 31 proceeds via the 1,2-acetoxonium ion 27, which may arise directly from the tetra-*O*-acetyl- α -D-mannopyranosyl bromide 25 through an anchimerically assisted dissociation. Traces of water present in the reaction mixture may then react with the ion 27 to form the orthoacid 28 which can rearrange either to 1,3,4,6-tetra-*O*-acetyl- β -D-mannopyranose (29) or 2,3,4,6-tetra-*O*-acetyl- β -D-mannopyranose (30). Under the conditions of the experiment, compound 30 is expected to anomerize to the thermodynamically favored α -anomer 31 and indeed only the compound 31 was isolated from the reaction mixture. Bonner and coworkers (101) studied the mutarotation of the three tetra-acetates 29, 30 and 31 in aqueous solution and found that 29 isomerized very slowly to yield 31, whereas 30 was comparatively faster to yield the same product.

It would be expected that a cyclic acetoxonium ion such as 27 would react very quickly with nucleophiles present in the reaction mixture. Thus, nucleophilic attack by imidazole on 27 could yield the *exo*- and *endo* orthoamides 34 and 35, respectively. Perlin (102,103) has described the preparation of the analogous diastereoisomeric 1,2-orthoesters of D-mannose under Koenigs-Knorr conditions. The present work shows that both the *exo* and *endo* isomers 34 and 35 are formed from tetra-*O*-acetyl- α -D-mannopyranosyl bromide 25. The method used differed from that used for the preparation of the *N*-mannosides in that, triethylamine was added to the reaction mixture, and the reaction was conducted at room temperature instead of heating under reflux (Table 8B).

Diagram 3





Thin layer chromatographic monitoring of the reaction showed that the starting material 25 had completely disappeared in 6 h, and workup using standard procedure gave a syrup, the n.m.r. spectrum of which showed two doublets in the region τ 4.4 to 4.55. One of these doublets was centered at τ 4.49 with a spacing of 2.6 Hz while the other at τ 4.53 had a spacing of 2.3 Hz. These signals were interpreted as being due to the anomeric protons of the *exo* and *endo* orthoamides 34 and 35. The integrated signals for the anomeric protons showed that the orthoamides were formed in a 2:1 ratio, the isomer having the anomeric doublet at τ 4.49 was present to the greater extent.

Although the two orthoamides have not been isolated individually as crystalline compounds, there appears little reason to doubt the proposed structure for the orthoamides. The n.m.r. spectrum of the product obtained as described above was quite different from that of the

TABLE 8

A study of the reaction of tetra-*O*-acetyl- α -D-mannopyranosyl bromide (25) with imidazole^a

Reaction No.	Reaction conditions	Temp. °C	Time	Yield, %			Ratio of		Remarks
				29 and 31	32	33	34 & 35		
A	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖] added	Reflux	4 h	7	30	20	-		b
B	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖] and	25	6 h	-	-	-	2:1		c
	2.5 mmoles of (C ₂ H ₅) ₃ N added			-	-	-	2:1		c
C	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖]	25	16 h	-	-	-	~1:1		c
	2.5 mmoles of (C ₂ H ₅) ₃ N added								
D	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖] and	25	7 days	-	-	-	~1:1		c
	2.5 mmoles of (C ₂ H ₅) ₃ N added								
E	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖] added	25	12 h	-	-	-	2:1		c
F	2.5 mmoles of (n-Bu) ₄ N [⊕] Br [⊖] added	25	40 h	-	small quantities		2:1		c
G		25	10 h	-	-	-	2:1		c
H		Reflux	4 h	-	60	40	-		c

^aAll reactions were carried out with 2.5 mmoles of 25 and 5 mmoles of imidazole in 5 ml of acetonitrile. Other conditions are given below.

^bRepresents recovered yields based on the starting material.

^cRepresents ratio of compounds as determined from the n.m.r. spectrum.

Table 8 (continued)

<u>29</u>	1,3,4,6-Tetra- <i>O</i> -acetyl- β -D-mannopyranose
<u>31</u>	2,3,4,6-Tetra- <i>O</i> -acetyl- α -D-mannopyranose
<u>32</u>	1-(Tetra- <i>O</i> -acetyl- α -D-mannopyranosyl)-imidazole
<u>33</u>	1-(Tetra- <i>O</i> -acetyl- β -D-mannopyranosyl)-imidazole
<u>34 and 35</u>	Tri- <i>O</i> -acetyl-1,2- <i>O</i> -(1- <i>N</i> -imidazolyl ethylidene)- β -D-mannopyranose, <i>exo</i> and <i>endo</i> isomers, respectively

α - and β -*N*-mannosides 32 and 33 (e.g. the anomeric proton absorptions for the orthoamides 34 and 35 were at a higher field than for the α - and β -*N*-mannosides 32 and 33; c.f. Fig. 5, 12 and 15).

When the reaction mixture was allowed to stand at room temperature for 16 h (Table 8C), the n.m.r. spectrum (Fig. 5) showed the presence of two orthoamides 34 and 35 in almost equal amounts. Even after a reaction period of 7 days at room temperature (Table 8D), the isomers 34 and 35 were still present in this ratio, indicating that the portion of the equilibrium had not changed.

The 100 MHz n.m.r. spectrum of the 1:1 mixture of the orthoamides 34 and 35, as shown in Fig. 5, exhibited two doublets at τ 4.49 with a spacing of 2.6 Hz and at τ 4.53 with a spacing of 2.3 Hz. These signals were assigned to the anomeric protons of 34 and 35, respectively. The *exo* configuration is assigned to 34 on the basis that it forms more rapidly than 35. However, as shown above, after a reaction time of 16 h, a 1:1 mixture of the orthoamides was obtained indicating that these compounds differ little in stability. Irradiation at τ 4.49 (H_1') collapsed a triplet at τ 5.66 (H_2') to a doublet with a spacing of 3.5 Hz ($J_{2',3'}$). The other coupling constants for the ring protons could not be determined due to the complexity of the spectrum. Perlin (102) correlated the chemical shifts for the ring protons of the *exo* and *endo* orthoesters of D-mannose. The anomeric proton and the C_2 -proton for the *exo*-orthoester were appreciably less shielded when compared with those of the *endo* orthoester. In the present study no such relationship has been observed, as for the anomeric proton at τ 4.49, H_2' appears at τ 5.66 and for the other isomer 35, H_1' is centered at τ 4.53 and H_2' at τ 5.48.

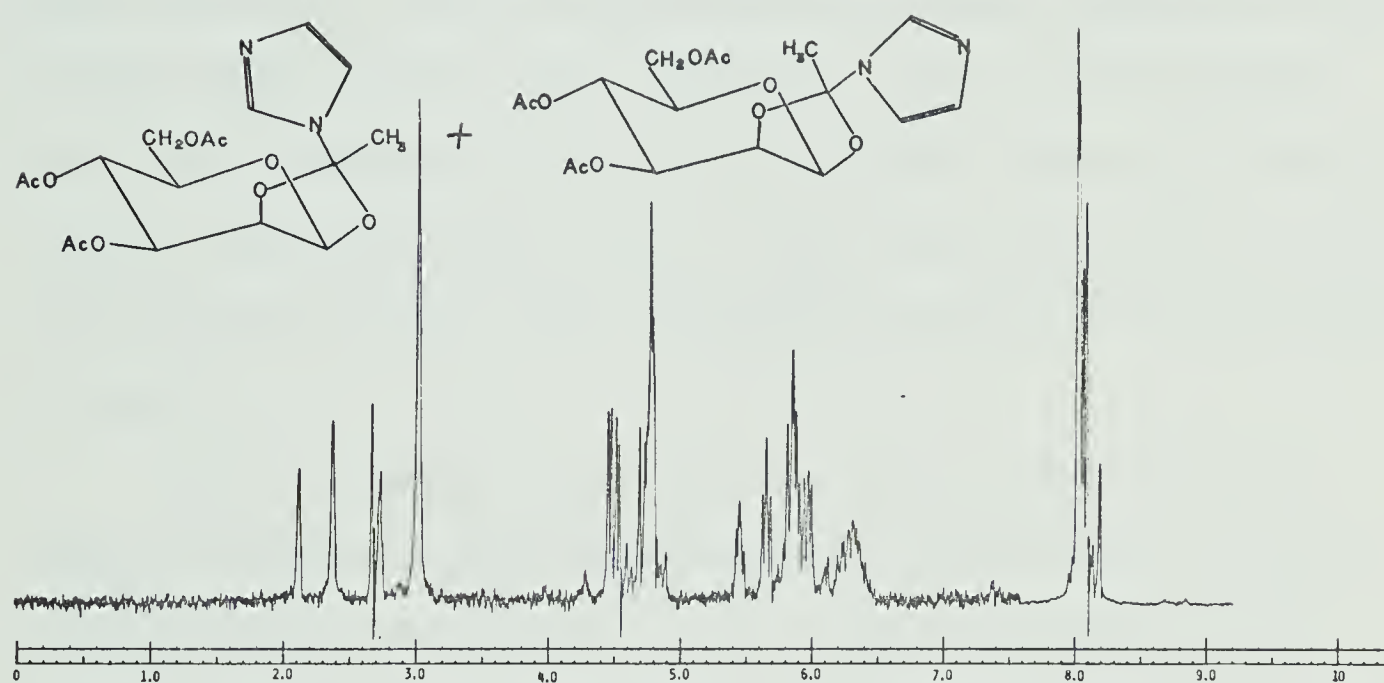


Fig. 5. N.m.r. spectrum (100 MHz) of tri-*O*-acetyl-1',2'-*O*-(1-*exo* and *endo*-*N*-imidazolyl ethylidene)-β-D-mannopyranoses (34 and 35) in deuteriochloroform. [Experimental 19 (ii)].

In the case of the *gluco*-orthoamides 23, previously discussed (p. 63), the observed $J_{1',2'}$ value indicated considerable pyranose ring flattening. This has also been shown to be true in the case of *gluco*-orthoesters (96). However, in the case of *manno*-orthoamides, the $J_{1',2'}$ coupling constant observed (2.6 and 2.3 Hz) suggests a $H_{1'}-C_{1'}-C_{2'}-H_{2'}$ structure having a dihedral angle of $\sim 57^\circ$ between $H_{1'}$ and $H_{2'}$. The value of $J_{1,2}$ for the *manno*-orthoester has been observed to range from 2.7 to 3.0 Hz (103). This would mean that the pyranose ring of the *manno*-orthoamides is not as distorted from the chair conformation as in the case of the epimeric *gluco*-orthoamide. This is understandable because the flattening of the pyranose ring would eclipse O_2' and O_3' of the *manno* orthoamide, thus causing a severe interaction, whereas in the case of *gluco* orthoamide such flattening increases the distance between O_2' and O_3' .

When the base, triethylamine, was omitted and the reaction allowed to proceed at room temperature for 12 h (Table 8E), all the starting material had reacted (t.l.c.). The n.m.r. spectrum of the isolated product showed the presence of the isomers 34 and 35 in a 2:1 ratio. When the reaction was performed for 40 h (Table 8F), some α - and β -*N*-mannosides 32 and 33 had started to form, but the orthoamides were still present in a 2:1 ratio. The effect of temperature is apparent from the reaction A and E (Table 8) when the reaction (A) was carried out at the refluxing temperature of the solvent for 4 h only α - and β -*N*-mannosides were formed, whereas a repeat of the reaction but at room temperature (E) for 12 h gave only the orthoamides 34 and 35. Finally the reaction was studied without the added tetra-*n*-butylammonium

bromide. After 10 h at room temperature (Table 8G), the reaction was complete and the orthoamides 34 and 35 were again present in a 2:1 ratio. This experiment is significant in that it suggests that the bromide ion, as one might have expected on theoretical grounds, plays no part in the formation of the orthoamides 34 and 35. This is in contrast to the *gluco*- series where it is definite that the presence of bromide ion accelerates considerably the rate of disappearance of the starting material, α -bromide 12, and thus the rate of formation of the orthoamides 23 and 24. This is understandable when the configurations at C₁' and C₂' are considered. The formation of the cyclic acetoxonium ion may proceed directly from the starting α -bromide 25 in the mannose case (*trans* coplanar arrangement of C₂ acetoxy and C₁-bromine atom), whereas, in the glucose case, the presence of bromide ion is required to catalyze the anomerization essential for the formation of the acetoxonium ion. In another reaction tetra-*O*-acetyl- α -D-mannopyranosyl bromide 25 and imidazole were heated under reflux for 4 h. The n.m.r. spectrum of the product showed the presence of α - and β -*N*-mannosides 32 and 33, respectively in a 3:2 ratio. Neither residual starting material 25 nor the orthoamides 34 and 35 were detected.

The variation in the ratios of the β -manno orthoamides 34 and 35, in the presence of the added base, as determined by n.m.r. spectroscopy is difficult to rationalize, but it appears that the initial 2:1 ratio is the result of the kinetic control of the reaction, whereas at equilibrium the ratio is 1:1. In the absence of added base, the equilibrium ratio remains 2:1. In related studies, Perlin (102) has reported the formation of *exo* and *endo*-tri-*O*-acetyl-1,2-*O*-(1'-methoxyethylidene)- β -D-mannopyranoses in the ratio of 3:2, by the reaction of the

tetra-*O*-acetyl- α -D-mannopyranosyl bromide with methanol in the presence of silver oxide. He similarly obtained the 1,2-(benzyl orthoacetates) in a ratio of 2:1 in favor of the *exo*-isomer.

In order to gain insight into the conformational properties of biologically important pyrimidine and purine nucleosides, a study of the effects of protonation and *N*-methylation on the conformation of *N*-D-ribofuranosyl imidazoles was made. For this purpose the required anomers of *N*-D-ribofuranosyl imidazoles were synthesized. Reaction of anhydrous hydrogen bromide with tetra-*O*-acetyl- β -D-ribofuranose (36) in methylene chloride led to an anomeric mixture of tri-*O*-acetyl-D-ribofuranosyl bromides 37 and 38. That these were formed in approximately equal amounts was ascertained from the n.m.r. spectrum of the mixture (Fig. 1), which showed a doublet at τ 3.26 with a spacing of 4.2 Hz for the anomeric proton of the α -anomer 37, and a singlet at τ 3.67 for the anomeric proton of the β -anomer 38. In different batches, the ratio of these anomers varied from 1:1 to 3:2 in favor of the β -anomer. Besides the presence of 37 and 38, the spectrum also indicated that about 5% of starting material 36 was still left in the mixture. Due to the instability of these ribofuranosyl bromides this anomeric mixture was used for the condensation reaction with imidazole without further purification.

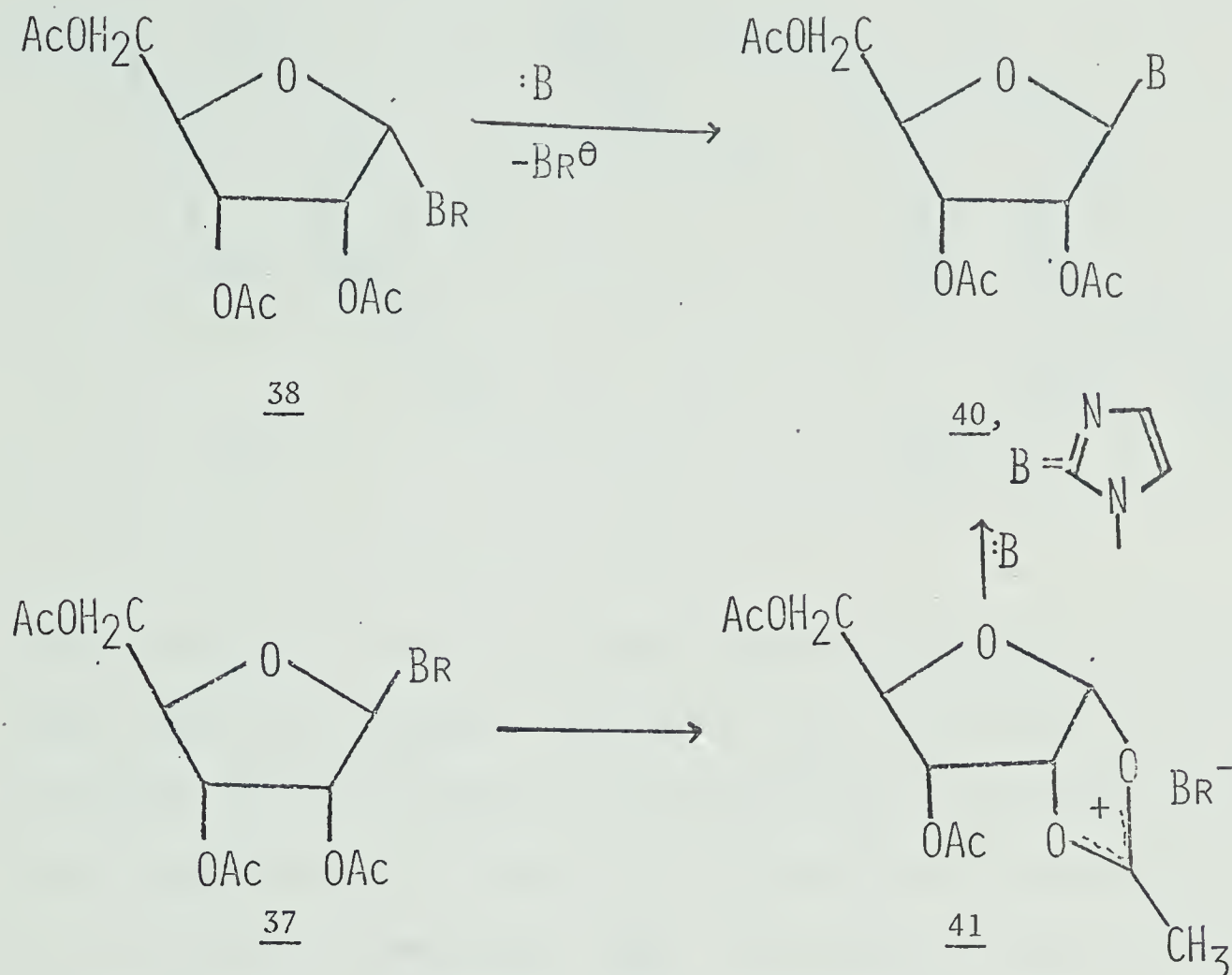
When the ribofuranosyl bromides 37 and 38 and imidazole were heated under reflux in acetonitrile for 3 h, both 1-(tri-*O*-acetyl- α -D-ribofuranosyl)-imidazole (38) and 1-(tri-*O*-acetyl- β -D-ribofuranosyl)-imidazole (40) were produced in yields of 4 and 45%, respectively. These were separated by column chromatography. The n.m.r. spectrum of

39 is reproduced in Fig. 32 and the parameters are presented in Table 31. The anomeric proton appeared at τ 3.70 as a doublet with a spacing of 5.2 Hz when the spectrum was run in deuterated dimethylsulfoxide. On the other hand, the n.m.r. spectrum of 40 (Fig. 27) showed the H_1' absorption at τ 4.0 as a doublet with a spacing of 5.4 Hz. It is apparent that on the basis of the observed magnitudes of $J_{1',2'}$ alone, it is difficult to assign the configuration at the anomeric center. Since the chemical shift for the anomeric proton can successfully be used to assign the configuration at the anomeric center (5,104), the H_1' absorption appearing at lower field is assigned to the anomeric proton of the α -anomer. Thus, α -configuration was assigned to the compound 39 and β -configuration to 40. Furthermore, the high *dextro* rotation, $+103^\circ$, observed for 39 as compared to -22° for the β -anomer 40 is in accord with this assignment. The rationale for the formation of two anomers 39 and 40 could be as follows: Firstly the α -bromide 38 can undergo a nucleophilic attack by imidazole with inversion of configuration at the anomeric center to give the β -*N*-riboside 40. Similar nucleophilic attack of imidazole on the β -bromide 37 can furnish the α -*N*-riboside 39. Since the starting material was a 1:1 mixture of the anomeric furanosyl bromides 37 and 38, one would have expected the product to be also a 1:1 mixture of the anomeric *N*-ribosides 39 and 40. Instead, this was not observed; the β -*N*-riboside 40 was formed in 45% where the α -anomer in only 4% yield. The possibility, that the α -*N*-riboside 39 is anomerizing to the β -anomer 40 under the reaction conditions employed was considered. This was found not to be the case because, when the α -*N*-riboside 39 was refluxed with equimolar amount of

imidazole hydrobromide followed by the usual workup procedure, the starting material 39 was recovered unchanged, and the presence of even small amounts of the β -*N*-ribose 40 could not be detected by n.m.r. spectroscopy.

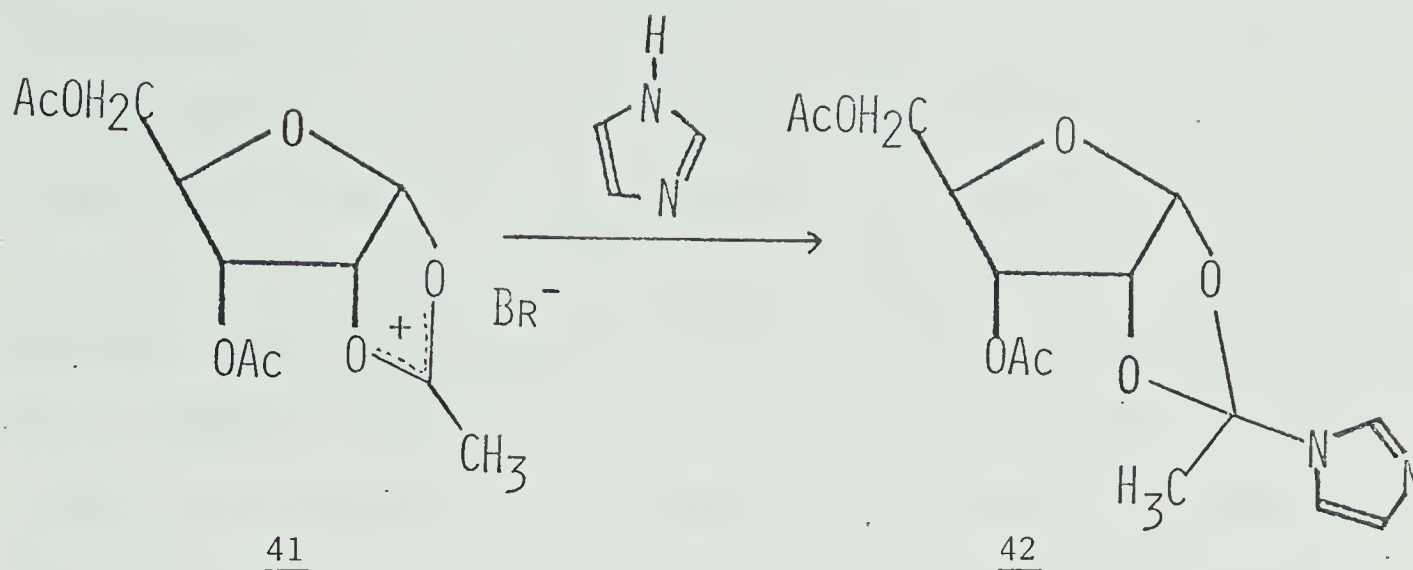
All the early syntheses of nucleosides (both ribosides and glucosides) yielded exclusively the β -anomer irrespective of whether the glycosyl halide had α - or β -configuration or was a mixture of the two. To account for this phenomenon Baker (88) proposed the " C_1'/C_2' *trans* rule" according to which the reaction between a hetero base and a glycosyl halide possessing a participating C_2' substituent always resulted in the formation of 1',2'-*trans* nucleoside. There have been exceptions to the "*trans* rule" and the formation of some α -nucleosides in these cases was attributed to the presence of β -glycosyl halide, a portion of which underwent a single S_N2 displacement (104,105). The *cis*-glycosyl halides (such as 38) react by a simple S_N2 reaction to give the β -nucleosides (e.g. 40, Diag.4). On the other hand the *trans*-glycosyl halides (such as 37) first undergo the intramolecular displacement of the bromide ion to yield the 1',2'-acetoxonium ion (e.g. 41) involving the participation of the neighboring 2'-acyloxy group. Then the acetoxonium ion 41 can undergo a second S_N2 reaction with base to give the β -nucleoside (e.g. 40). The formation of 1,2-*trans* nucleoside in larger proportion with respect to the 1,2-*cis*-anomer has indeed been observed in this study. However, this was also observed in the studies related to gluco- and mannopyranosyl imidazoles, already discussed, but the 1,2-*trans*/1,2-*cis* ratio was much smaller. It may be assumed, that these differences originate largely in the different reaction properties

Diagram 4



of furanosyl halides as compared to the pyranosyl halides.

The formation of the acetoxonium ion 41 under the experimental conditions employed is highly probable, and one would expect the reaction of imidazole with the ion 41, to yield an orthoamide such as 42. In order to present some evidence that such an orthoamide is produced, the reaction was carried out at moderate temperatures. When the 1:1 anomeric mixture of tri-*O*-acetyl-D-ribofuranosyl bromides 37 and 38 was reacted with imidazole at 0° , the reaction was complete in 30 min. The reaction product was isolated using the standard workup procedure and its n.m.r. spectrum exhibited one doublet centered at τ 3.95 with a



spacing of 4 Hz, a doublet with some long range splittings at τ 4.13 with a width of ~ 5 Hz, and a singlet at τ 3.84. The doublet at τ 4.13 was due to the β -*N*-riboside 40 which had already been characterized by n.m.r. spectroscopy. The singlet at τ 3.84 was due to the unreacted tetra-*O*-acetyl- β -D-ribofuranose (36). The presence of any α -*N*-riboside 39 giving rise to a doublet at τ 3.80 could not be detected and it is possible that a very small amount of 39 may have been formed. Thus the doublet at τ 3.95 with a spacing of 4 Hz may be attributed to the anomeric proton of the orthoamide 42. This assignment was substantiated by observing two sets of signals for the imidazole ring protons in the region τ 2.2 to 3.2; those at τ 3.03 (H_4 , H_5) and 2.4 (H_2) of the β -*N*-riboside 40 and at $\sim \tau$ 2.7 (H_4 , H_5) and 2.26 (H_2) of the orthoamide 42. The compounds 40 and 42 were present in 3:1 ratio, respectively.

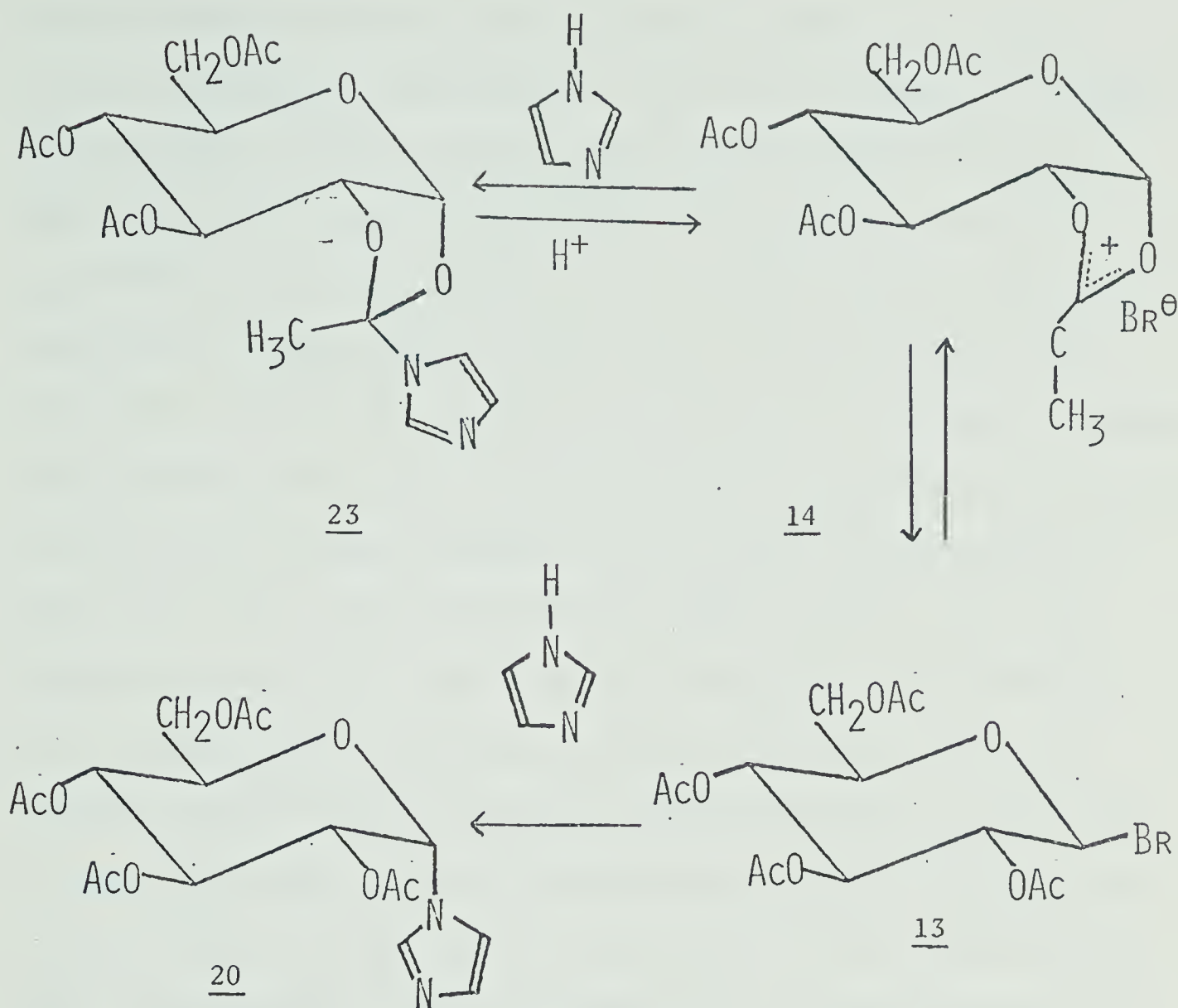
When the reaction mixture was allowed to stand at 0°C for 4 h, the n.m.r. spectrum of the product showed the presence of 40 and 42 still in 3:1 ratio, respectively. Again the presence of the

α -*N*-riboside 39 could not be detected. Reaction at room temperature for 4 h gave a product, the n.m.r. spectrum (Fig. 2) of which, showed the presence of the α -*N*-riboside 40 and orthoamide 42 in 4:1 ratio, respectively. The doublet at τ 3.8 with a spacing of 5.5 Hz, due to the α -*N*-riboside 39 (4%), was also observed. Finally the reaction was performed at the refluxing temperature (acetonitrile as solvent) for 3 h. The product was fractionated by column chromatography and the following products were obtained: 1-(tri-*O*-acetyl- α -D-ribofuranosyl)-imidazole (39, 4%); 1-(tri-*O*-acetyl- β -D-ribofuranosyl)-imidazole (40, 45%) and tetra-*O*-acetyl- β -D-ribofuranose (36, 5%).

The formation of only one orthoamide was observed in the present study of the ribose series. This is quite understandable, if one examines the molecular models of these compounds. The imidazole ring and the C₃'-acetoxy group in the *endo*-orthoamide are too close to each other, to allow its formation. The attack of imidazole ring on the 1,2-acetoxonium ion from the *trans*-side should be favored, thus yielding the *exo*-orthoamide 42.

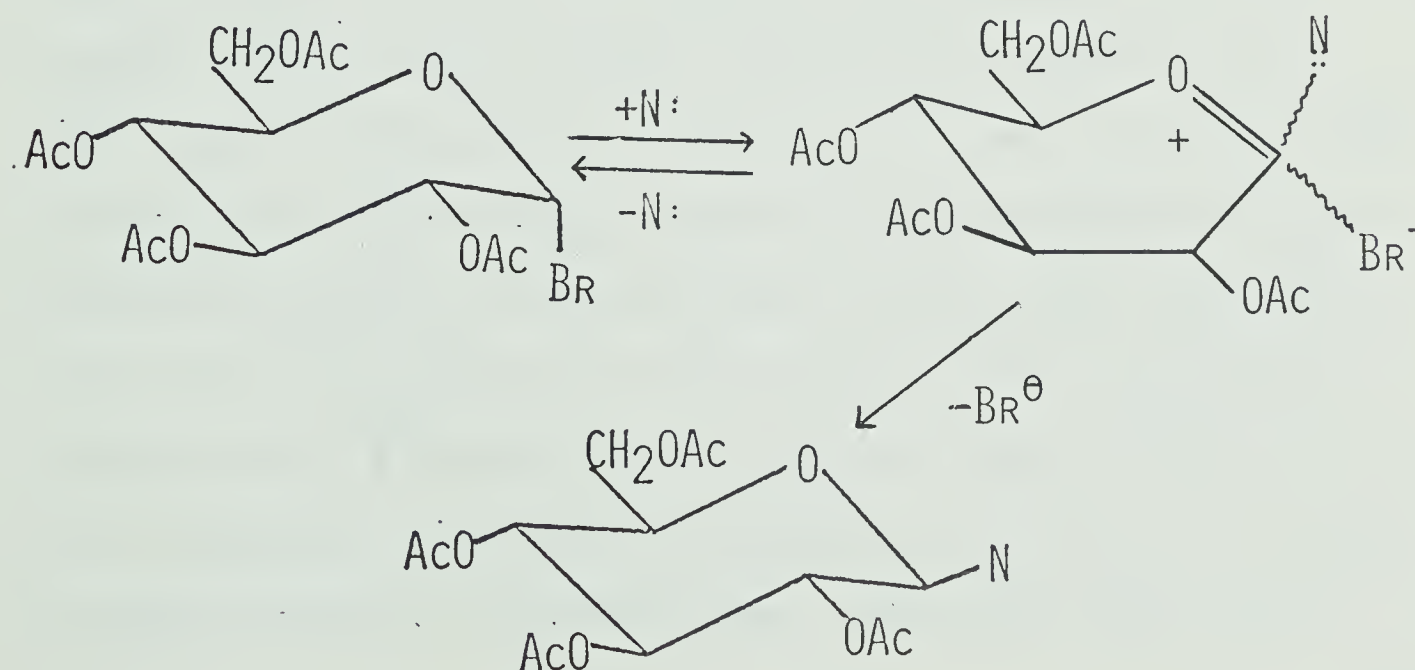
The mechanism as to how the *N*-glycosyl imidazoles are formed from the acetylated glycosyl bromides may be considered in the following manner. When tetra-*O*-acetyl- α -D-glucopyranosyl bromide (12) was heated with imidazole in acetonitrile, the anomeric *N*-glucosides 20 and 21 were formed in a ratio of 1:1.2 in favor of the β -anomer 21, irrespective of whether tetra-*n*-butylammonium bromide was added to the reaction mixture or not. The 1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21) could be formed by a nucleophilic attack of the imidazole molecule on the α -bromide 12, resulting in concomitant inversion of configuration at

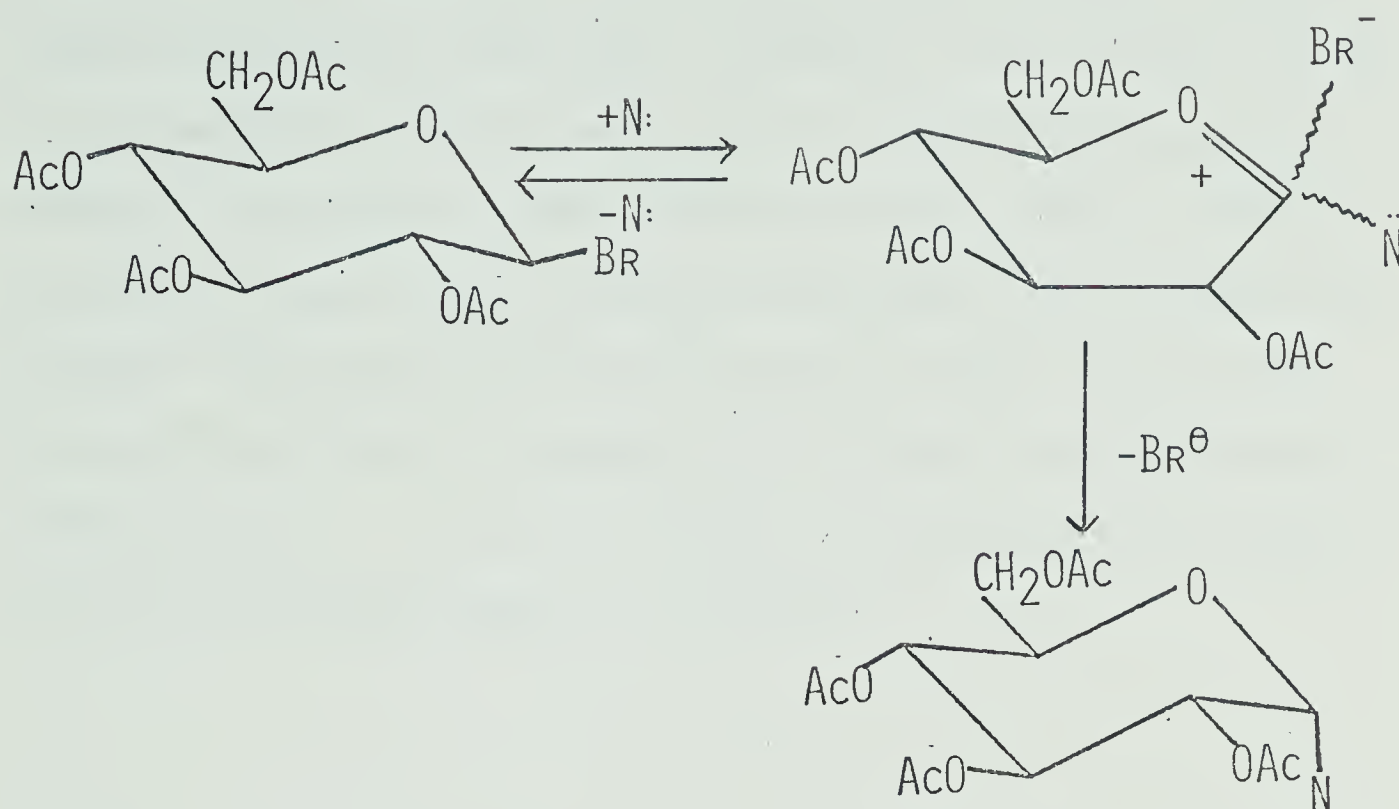
the anomeric center. Thus, the liberated bromide ion is expected to anomerize the α -bromide 12 to its β -anomer 13 (77), which in turn could undergo a nucleophilic attack by imidazole to furnish the 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20). At the same time the β -bromide 13 is expected to undergo an anchimerically assisted ionization to yield the 1,2-acetoxonium ion 14 (77). This ion by capturing a molecule of imidazole, could lead to the formation of the orthoamides 23 and 24. Although a rearrangement of the orthoamides to the α -*N*-glucoside 20 is theoretically likely, the possibility also exists that the orthoamides were converted back to the β -bromide 13, and that this latter compound is the true precursor of the α -*N*-glucoside 20. This would be in accord with recent investigations, which have established the preferential formation of α -glucopyranosides by way of a halide ion catalyzed reaction of tetra-*O*-benzyl- α -D-glucopyranosyl halide with alcohols in the presence of tertiary amines (106). Clearly, participation of the C₂-benzyloxy group cannot be invoked to guide the alcohol into the 1,2-*cis*- α -configuration. The α -glucoside in all probability arises from nucleophilic attack at the anomeric center of the β -halide, which is in equilibrium with its α -anomer. In the absence of evidence to the contrary and also since no evidence could be obtained in support of a direct "orthoamide" intermediate rearrangement, this course of reaction is assumed to prevail for the formation of the α -*N*-glucoside 20. In other words, it is considered that the acid catalyzed decomposition of the intermediate orthoamides 23 and 24 leads mainly to the β -bromide 13, which is thus regenerated and available for nucleophilic attack by imidazole.



It is reasonable to expect the equilibrium constant for the $\beta \rightleftharpoons \alpha$ equilibration of the tetra-*O*-acetyl-D-glucopyranosyl bromides to be about that, 16, found for the tetra-*O*-acetyl-D-glucopyranosyl chlorides (77). Assuming that α -glucosides arise exclusively from nucleophilic attack of imidazole on the β -bromide 13 and the β -glucosides from nucleophilic attack on the α -bromide 12, then the rate of attack by imidazole on the β -bromide is in the order of (16×0.83) 13 times faster. In the case of pyridine (90), the β -bromide would react about (16×9) -144 times faster. This difference in relative

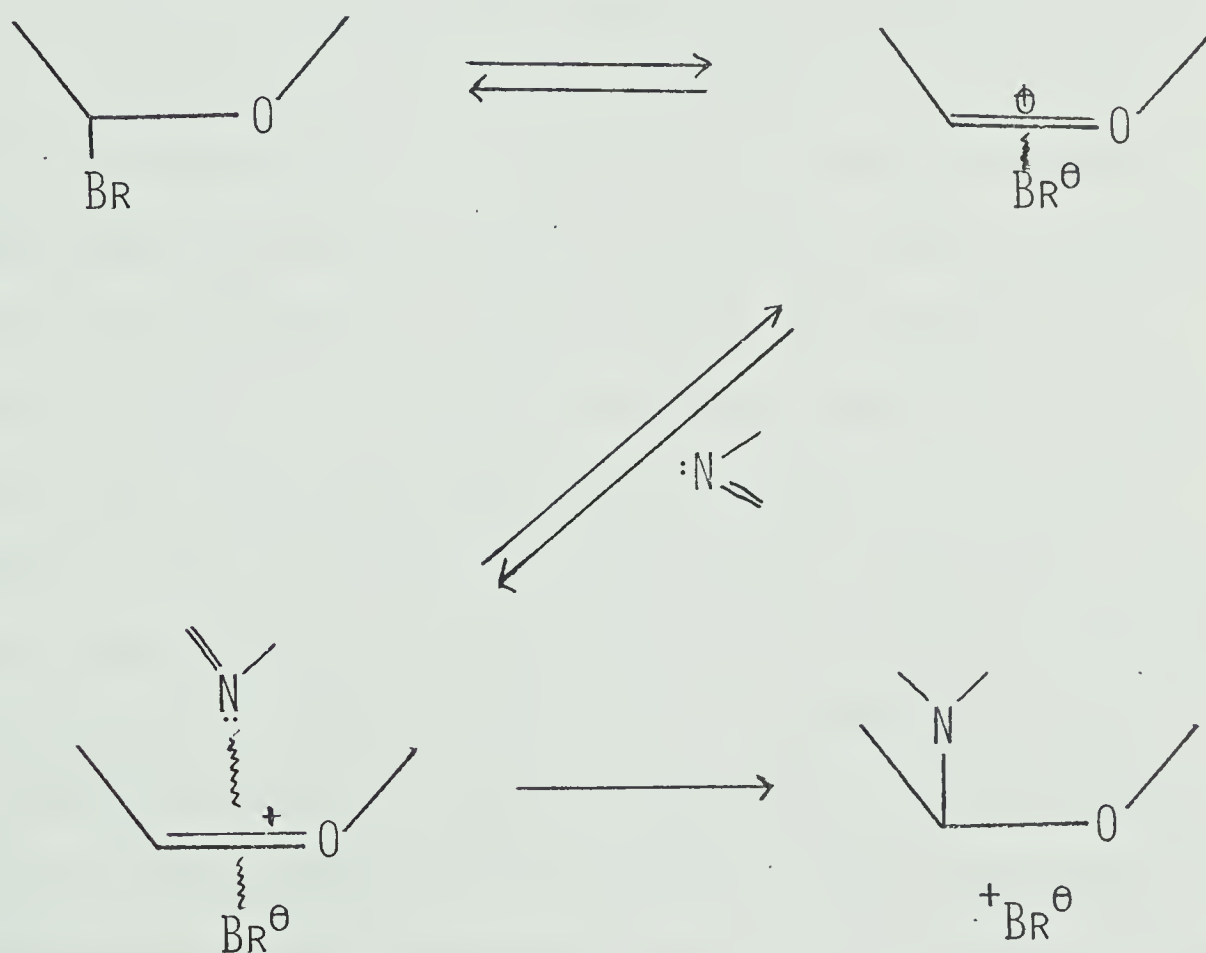
rates presumably would arise mainly from the difference in nucleophilicity of imidazole and pyridine. The point of interest is that, in both cases, the β -bromide would be the much more reactive anomer, in spite of the fact that it is the anomer with the bromine atom in equatorial orientation. Ordinary considerations based on the steric requirements for S_N2 mechanism, would lead to the anticipation of a more facile nucleophilic attack at the anomeric center of the α -bromide, since the rear-side of the C-Br bond is exposed for attack, whereas this is not the case for the β -bromide in the absence of a conformational change that would require considerable energy. However, these considerations do not likely apply to the reaction of an α -haloether, as is represented by the glycosyl halides, since these halides are strongly activated toward replacement of the halogen by participation of the geminal oxygen atom in delocalizing the positive charge at the anomeric center which develops in dissociation of the C-halogen bond. Thus, as suggested by Lemieux and Hayami (77), the intermediates for these reactions are likely to be ion-pair molecule triplets as shown below.





It is of interest to note, that the β -bromide 13 is much more reactive than the α -anomer 12, and that these compounds are rapidly interconverted by bromide ion at a rate which is considerably faster than their reactions with the base. Thus, the β -bromide may be a trivial intermediate in the reaction of the much more thermodynamically stable α -anomer. There would then remain the question of why the β -anomer is so much more reactive. Experimental evidence to this effect can be inferred from the observation by Lemieux and Huber (107) that 3,4,6-tri-*O*-acetyl- β -D-glucopyranosyl chloride undergoes acetolysis, under a variety of conditions, about 100 times more rapidly than the α -anomer. The explanation would require a lower free energy of activation for the formation of the β -ion-pair molecule triplet than its α -counterpart, since these intermediates can reasonably be expected to readily collapse to the *N*-glucosides. The obvious basis for a

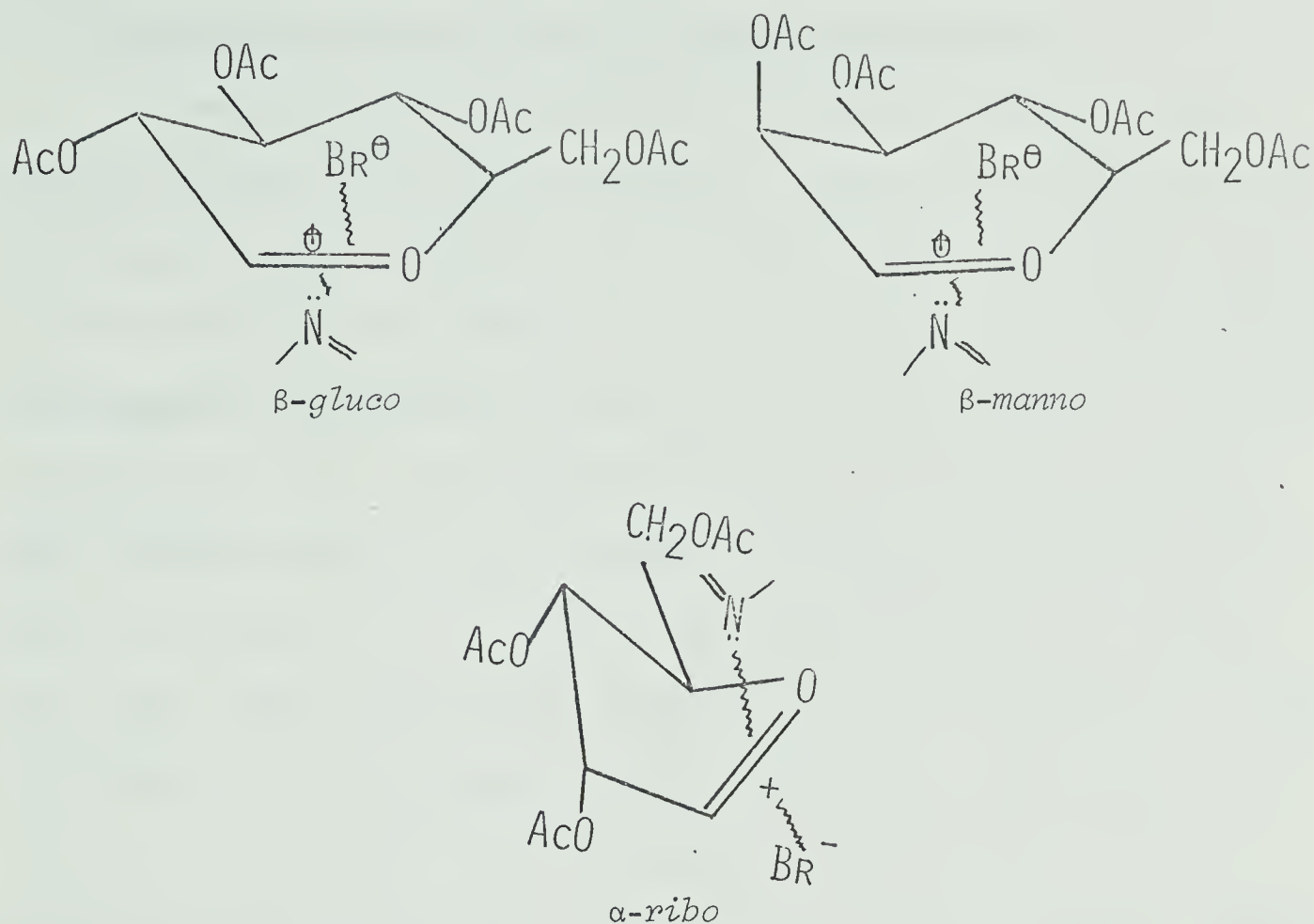
rationalization would then be to assume, that the β -ion-pair molecule triplet represents the more stable arrangement for the bromide ion and the base about the cationic center, and that this inherently greater stability is also found in the transition states. However, another possibility exists which is considered noteworthy. This envisages an important role played in the overall process by dissociation of the glycosyl bromide, prior to solvation by the base, to form the ion-pair molecule triplet. That is, the reaction is considered to proceed by way of the following sequence of equilibria.



Thus the rate of formation of the ion-pair molecule triplet would depend on the ease of dissociation of the C-Br bond to the ion-pair, the concentration of the base, and likely, to an important degree, on the ability of the base to stabilize the triplet structure, which could vary both for different glycosyl halides and different bases depending on the steric requirements. Thus, although the steady state ion-pair concentration for one anomer may be greater than for the other, this propensity for the reaction could be effectively cancelled by unfavorable structural requirements for the triplet. The second equilibrium would then be expected to dominate the route of reaction, should both halides lead to ion-pair at, or near, the same rate. Should, however, there be little difference between the relative stabilities of the anomeric triplets, then evidently the dispositions of the anomeric halides for dissociation to ion-pairs would reasonably be invoked as of prime importance in determining the preferred route of reaction. Of course, the formation of ion-pairs rather than separate ions is suggested because of their implication in the anomerization of the anomeric tetra-*O*-acetyl-D-glucopyranosyl chlorides by Lemieux and Hayami (77). The virtue of these speculations is simply that these offer an alternative way of interpreting the very limited information available, and the mechanistic possibility is presented basically for its heuristic value rather than an accomplishment of this research. The goals of this research were not directed towards such studies and, as a consequence, little data were accumulated with reference to these mechanistic possibilities. Nevertheless, it is considered of interest that this theory does allow a reasonable interpretation of data which

is not amenable to rationalization on the basis of either simple $\text{S}_{\text{N}}2$ type mechanistic considerations, or by way of acetoxonium ion intermediates. An interpretation is possible involving separated ions, but this interpretation would not account for the bromide-ion catalysis, unless it were assumed that one of the glucosyl bromides leads to an intimate ion-pair, which is not readily solvated by the base and which strongly resists ion separation, whereas the other anomer readily passes to separated ions. It seems difficult to envisage an ion-pair which is not highly susceptible to stabilization by a base, especially one in which the positive charge of the cation is delocalized over two adjacent atoms and involves a trigonal carbon atom. The products of these reactions are obviously the result of kinetic control since in the case of the bromide-ion catalyzed reaction of tetra-*O*-acetyl- α - D -glucopyranosyl bromide with pyridine, the main product (>90% yield), α -*N*-glucoside, is obviously several kilocalories per mole less stable than the β -anomeric pyridinium glucoside.

It is tempting, therefore, to offer the following rationalization. In the case of both the tetra-*O*-acetyl- D -gluco- and manno pyranosyl bromides, the β -anomer dissociates to a more stable ion-pair than does the α -isomer. Thus, the concentration of the β -ion-pair is high, and this leads to a tendency for the formation of α -*N*-glucoside. With imidazole as the base, solvation of the β -ion-pair, in the *manno* configuration is conceivably more favorable than for the α -ion-pair (relative to the *gluco* situation) in view of the axial disposition of the 2-acetoxy group and this could explain the slightly higher yield of α -*N*-glycoside in the case of the *manno* derivatives even though the

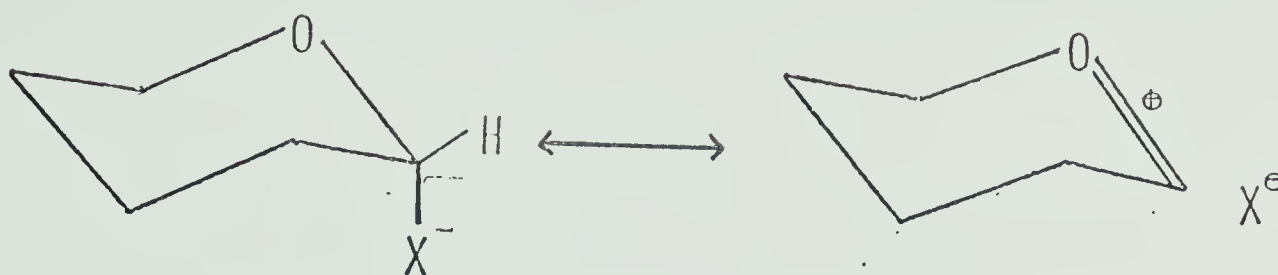


β -ion-pair should be less stable than the α -ion-pair. The high yield of β -*N*-riboside would follow similar reasoning. In this case, effective solvation of the α -ion pair by the base would be difficult for reasons of eclipsing with the 2-acetoxy group. Thus, from this point of view, the main feature guiding the preference for the route of reaction is the effectiveness of the stabilization of the ion-pair intermediates through solvation of these intermediates by the base prior to collapse of the resulting ion-pair molecule triplets to products.

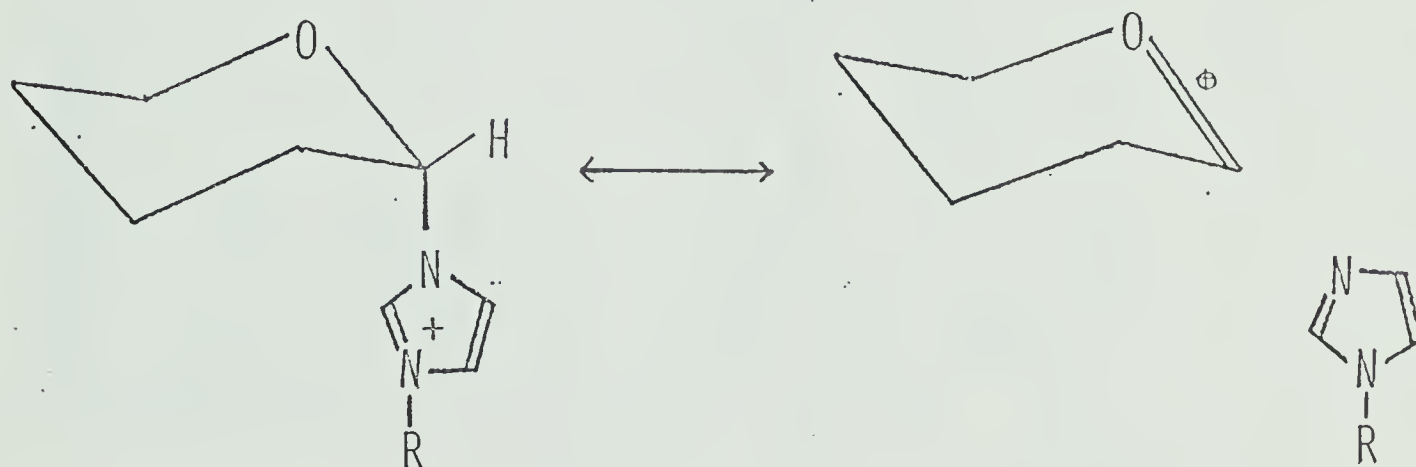
B. The reverse Anomeric Effect in *N*-Glycosyl Imidazoles

Whereas the previous section dealt with the synthesis and characterization of *N*-glycosyl imidazoles, this part is devoted to the discussion directed towards establishing the actual existence, if any, of the reverse anomeric effect. The anomeric effect is a more favorable arrangement of dipole-dipole interactions when the aglycon is in axial orientation (13,17). It was postulated that this might be reversed when the atom attached to the anomeric center carried a substantial positive charge (60). To date, it has not been possible to separate the steric from dipole-dipole interactions for the structures believed to exhibit the reverse anomeric effect (60,66,67). Since in all these cases very substantial steric effects are associated with the axial orientation of the aglycon, it has not been ascertained whether these are the only important driving forces for the molecule to adopt a conformation in which the aglycon takes up near equatorial orientation. For this reason an investigation of the effect of either protonation or alkylation of *N*-glycosyl imidazoles was undertaken. It was thought that this might provide information on the existence of the reverse anomeric effect for the following reasons: (i) the protonation or alkylation of the nitrogen atom of the imidazole ring remote from the anomeric center should not appreciably affect the steric interactions between the imidazole ring and the remaining substituents on the pyranose ring, (ii) the protonation or alkylation is not expected to appreciably shorten the C-N glycosidic bond. Indeed, if one of the prevailing theories for the origin of the anomeric effect, such as

stabilization as a result of "no-bond" resonance (42), is correct,



then one might expect the protonation or alkylation to enhance rather than weaken the anomeric effect. Such a lengthening of the C-N



glycosidic bond would not be expected to increase the steric interactions of the aglycon when it is protonated or alkylated.

Should the reverse anomeric effect exist, as pointed out by Lemieux and Morgan (60), the imidazole ring carrying the positive charge should prefer the equatorial orientation. Thus, the information gained on the conformational behavior of *N*-glycosyl imidazoles could contribute towards a greater understanding of the role of biologically important purine nucleosides in nature.

The anomeric proton of 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20, Fig. 6, Table 9) appeared as expected at the lowest

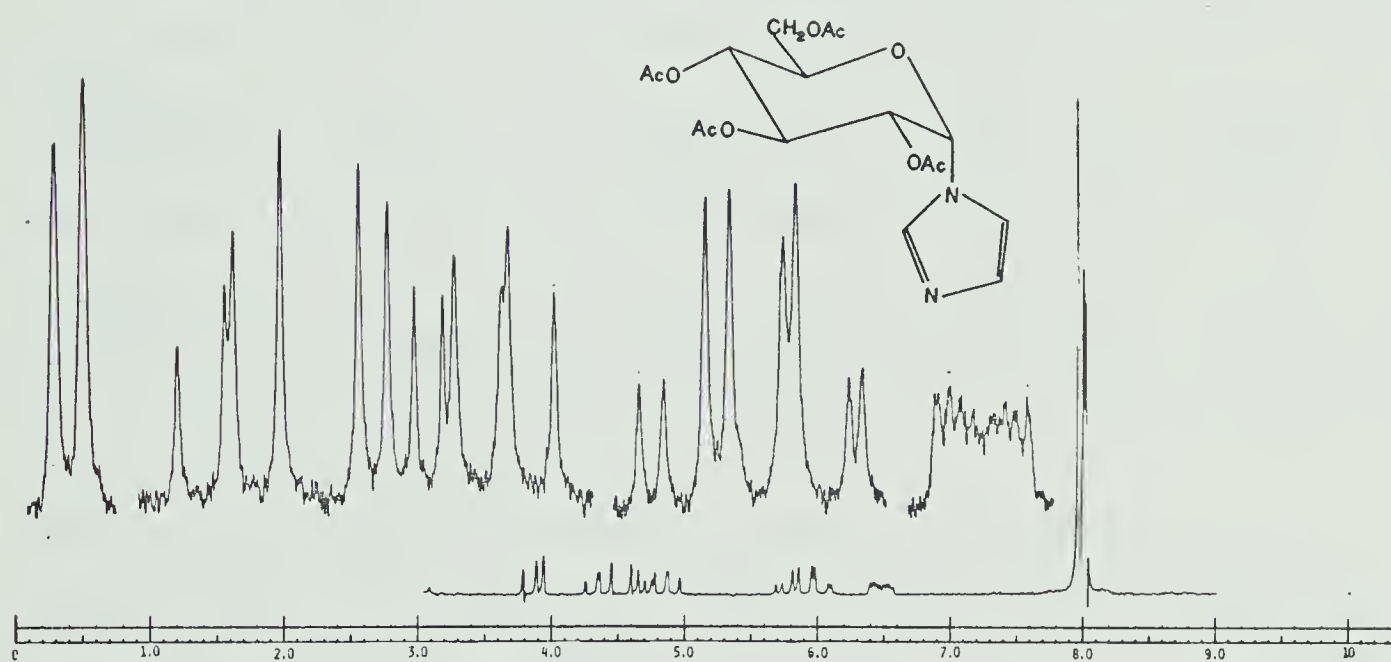


Fig. 6 N.m.r. spectrum (100 MHz) of 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20) in deuteriochloroform. Inset, sweep width 250 Hz.

field of all the pyranose ring protons, due to the deshielding effect of the geminal nitrogen and oxygen atoms. The coupling constants observed (Table 9) are in excellent agreement with those expected for the

TABLE 9

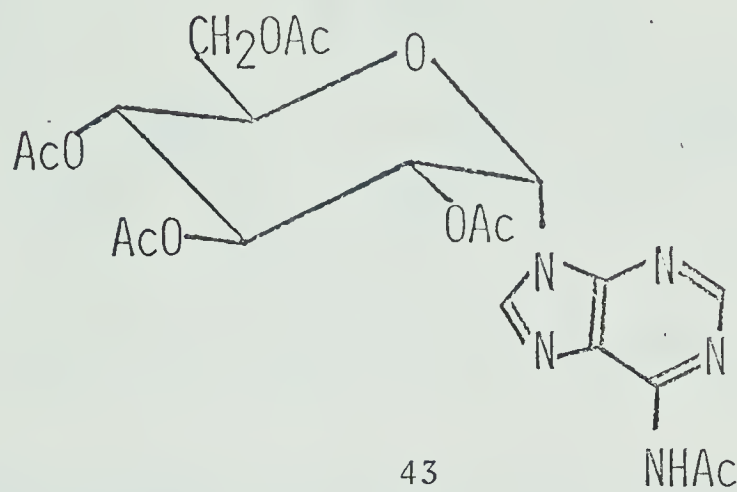
N.m.r. parameters (100 MHz) of 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20)

Solvent	H-1'	J _{1',2'}	H-2'	J _{2',3'}	H-3'	J _{3',4'}	H-4'	J _{4',5'}
	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)
Deuterio-chloroform	3.90(d)	5.3	4.66(q)	10.5	4.35(q)	8.2	4.84(q)	10.6
Chloroform	3.91(d)	5.3	4.68(q)	10.5	4.36(q)	8.5	4.87(q)	10.3
1,2-dichloro-ethane	3.98(d)	5.0	4.72(q)	10.2	4.46(q)	8.0	4.95(q)	10.3

compound 20 in the 4C_1 conformation, and with the imidazole group adopting near axial orientation. This is evident from the magnitudes of values for J_{2',3'}, J_{3',4'} and J_{4',5'} which require the hydrogens at positions 2',3',4' and 5' to be in axial orientation, indicating a projected angle of ca. 180° between the vicinal C-H bonds (109-111, 128, 147). However, the value of J_{1',2'} = 5.3 Hz (in chloroform) requires the hydrogens at positions 1' and 2' to define a dihedral angle of about 40°. The relief of the non-bonded interaction between the imidazole ring and the hydrogens at positions 3' and 5' must be expected to cause a distortion of the chair form of the pyranose ring, and this should lead to a decrease of the torsional angle between

H_1' and H_2' .

During the course of this study Onodera and coworkers (67) reported, that the structurally similar 6-acetamido-9-(tetra-*O*-acetyl- α -D-glucopyranosyl)-theophylline (43), showed a coupling constant of



5.7 Hz for $J_{1',2'}$ and 9.0 Hz for $J_{2',3'}$, $J_{3',4'}$ and $J_{4',5'}$, and therefore existed in the 4C_1 conformation. These values are similar to the ones found for 20 in this work.

The protonation of the imidazole ring was affected by adding varying amounts of trifluoroacetic acid (TFA) to a chloroform solution of the compound 20. The n.m.r. spectral data obtained for the resulting solution are summarised in Table 10. That the addition of one mole of TFA per mole of 20, in chloroform, had caused a conformational change from the 4C_1 conformation (Fig. 7), was apparent from the new coupling constants (Table 10). As previously mentioned (p.19), X-ray

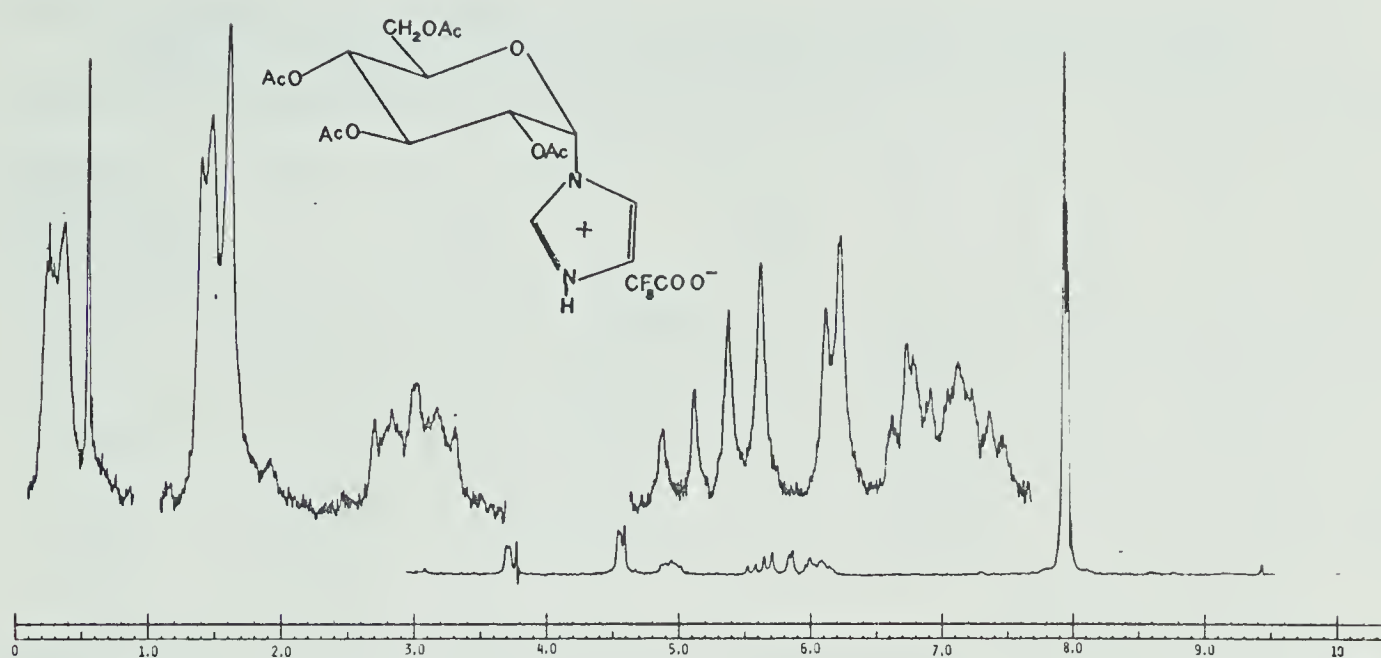


Fig. 7. N.m.r. spectrum (100 MHz) of 1-(tetra-*O*-acetyl-α-D-glucopyranosyl)-imidazole (20) in chloroform containing one molar equivalent of TFA. Inset, sweep width 250 Hz.

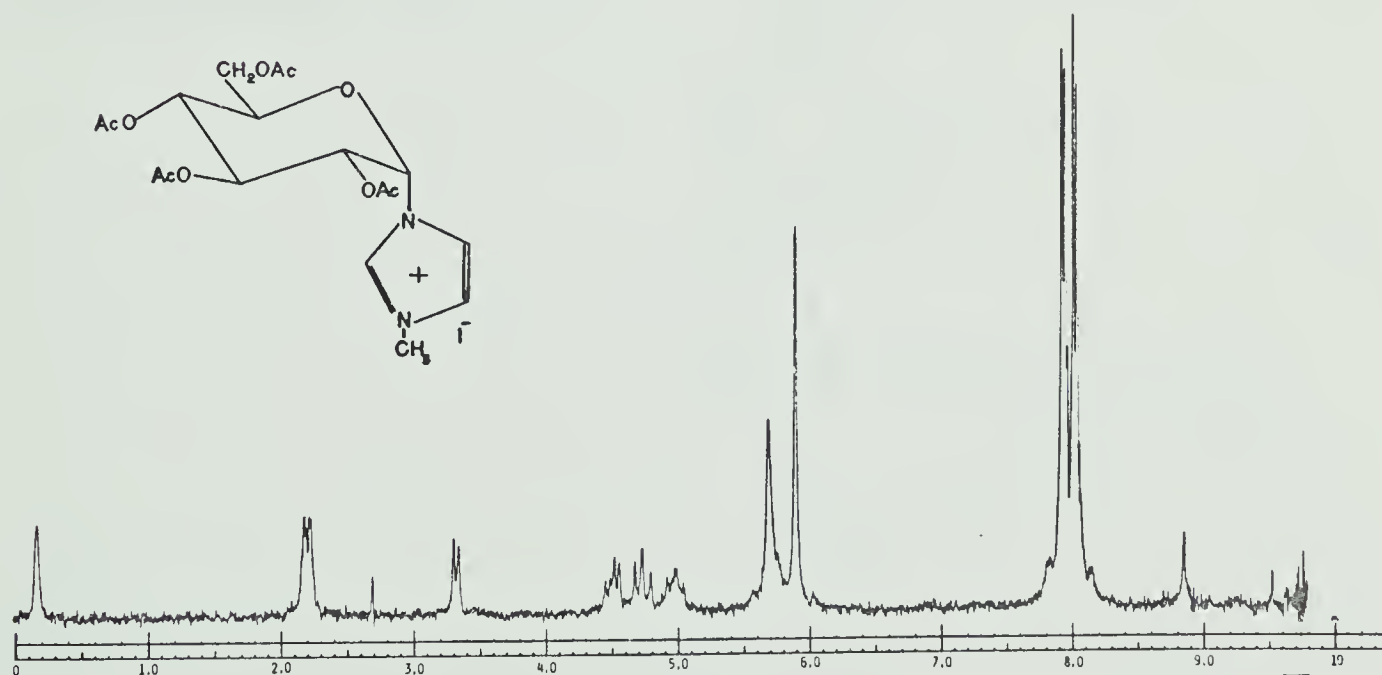


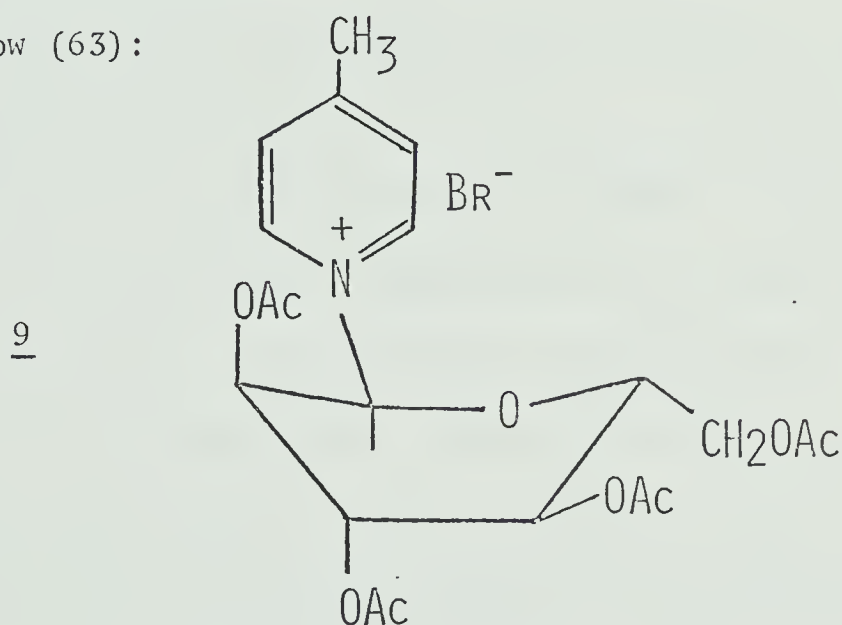
Fig. 8. N.m.r. spectrum (100 MHz) of 3-methyl-1-(tetra-*O*-acetyl-α-D-glucopyranosyl)-imidazolium iodide (44) in deuteriochloroform.

TABLE 10

N.m.r. parameters (100 MHz) of 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20) in CHCl_3 with varying amounts of TFA added

Mole TFA added per mole of <u>18</u>	H-1' (τ)	$J_{1',2'}$ (Hz)	H-2' (τ)	$J_{2',3'}$ (Hz)	H-3' (τ)	$J_{3',4'}$ (Hz)	H-4' (τ)	$J_{4',5'}$ (Hz)
0	3.91(d)	5.3	4.68(q)	10.5	4.36(q)	8.5	4.87(q)	10.3
0.25	3.81(d)	4.8	4.62(q)	9.2	4.44(q)	7.8	4.89(q)	9.2
0.50	3.81(d)	4.4	4.63(q)	8.7	4.47(q)	7.5	4.91(q)	8.8
1.0	3.71(d)	3.4	-	-	-	~ 5.6	4.94(m)	-

crystal structure analysis of 4-methyl-1-(tetra-*O*-acetyl- α -D-glucopyranosyl) pyridinium bromide (9), showed it to exist in the $^{2,5}_B$ conformation shown below (63):



The n.m.r. data viz. $J_{1',2'} = 2.8$ Hz, $J_{2',3'} = 3.1$ Hz, $J_{3',4'} = 3.2$ Hz and $J_{4',5'} = 5.7$ Hz supports the $^{2,5}_B$ conformation in solution as well. On the basis of this, one may expect the *N*-protonated compound 20 to adopt a boat conformation. For a $^{2,5}_B$ conformation, $J_{2',3'}$ and $J_{3',4'}$ should be of nearly the same magnitude but smaller than $J_{4',5'}$ and

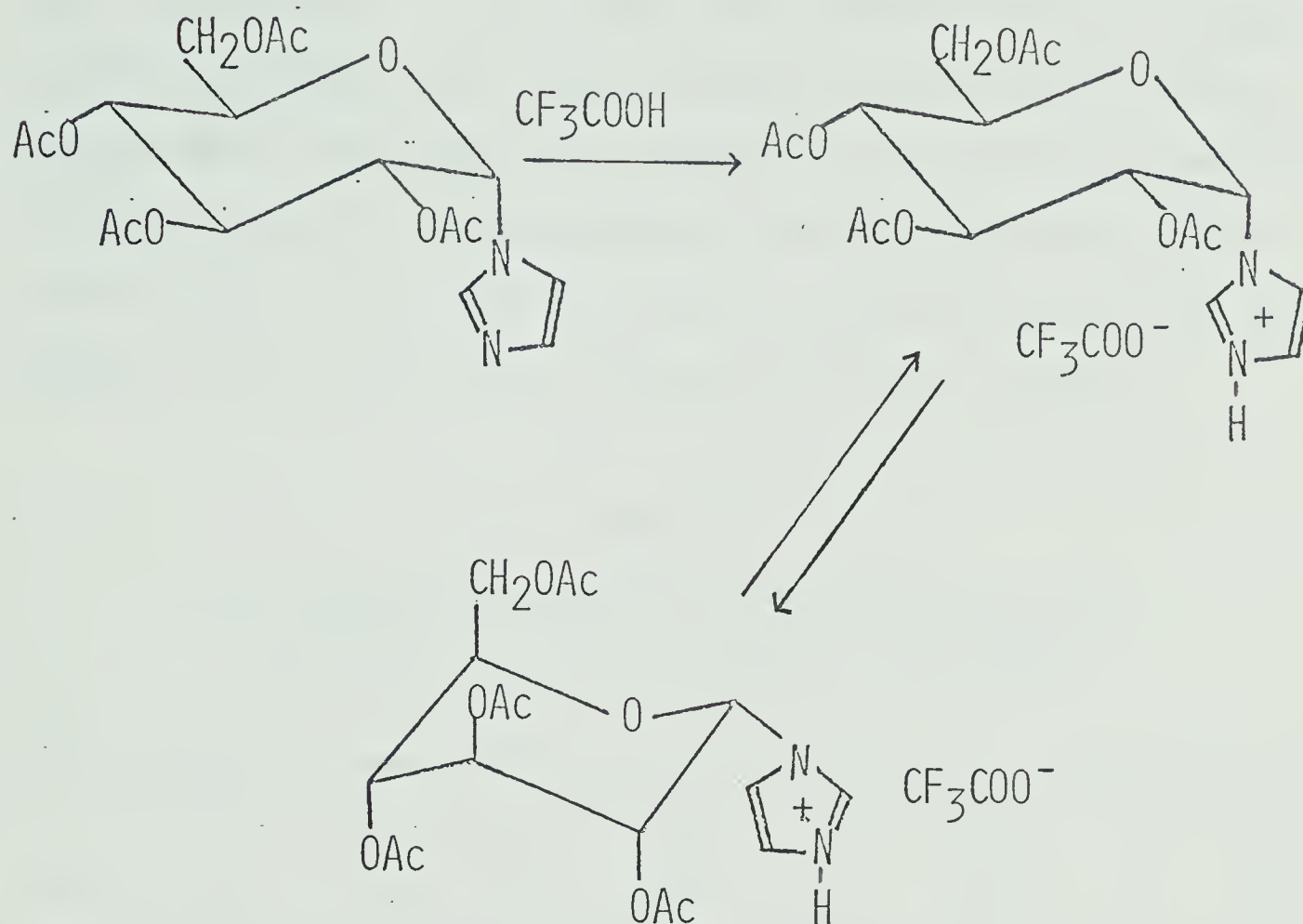
this indeed is observed for the pyridinium α -*N*-glucoside 9. As shown in Table 10, the coupling constants $J_{2',3'}$ and $J_{4',5'}$, observed when varying amounts of TFA were added to chloroform solution of 20, are of the same magnitude. On this basis, the presence of fully protonated 20 in ${}^{2,5}B$ conformation alone is ruled out. This line of argument, however, does not exclude the presence of protonated 20 in an equilibrium between 4C_1 and ${}^{2,5}B$ conformations. If this were so, one would observe the time averaged values for the coupling constants considered, and $J_{4',5'}$ would still be larger than $J_{2',3'}$ and $J_{3',4'}$. This is clearly not observed. Similarly the possibility of protonated 20 existing in an alternative boat conformation such as $B_{2,5}$, ${}^{1,4}B$, $B_{1,4}$, ${}^{0,3}B$ and $B_{3,0}$, or any one of these conformations in equilibrium with the 4C_1 conformation, was eliminated.

Realising that, apart from the isolated and coincidental cases, the only true chair or boat conformations are adopted by cyclohexane ring and various skew conformations represent only degrees of departure from the ideal cases, it is felt that a consideration of relevant skew conformations for protonated 20, or any equilibria involving those conformations, would not be of significance. Since one is dealing with the n.m.r. spectral data which are firstly subject to error and secondly are only one of a set of possible solutions to a mathematical equation, this self-imposed restriction stated above is felt to be justified.

Although the existence of fully protonated α -*N*-glucoside 20 in 1C_4 conformation alone is also not supported by the observed coupling constants, a solution may lie in the consideration of an equilibrium

between 4C_1 and 1C_4 conformations (Diag. 5), assuming that these are the only two major contributors.

Diagram 5



This equilibrium should be dependent on the extent of protonation of the imidazole ring, i.e., the concentration of the acid added. The experiments in which varying amounts of TFA were added resulted in a gradual change of the coupling constants ($J_{2',3'}$, $J_{3',4'}$ and $J_{4',5'}$ in Table 10), thus supporting the existence of the above mentioned conformational equilibrium.

If the conformation adopted by the pyranose ring is dependent

on the extent of protonation of the basic imidazole ring, then a relationship would be expected between the measured coupling constants and the strength of the acid added to effect protonation. Thus, one might expect that if equal quantities of a strong (e.g., TFA) and a weak (e.g., CH_3COOH) acid are added to the chloroform solution of 20, the weak acid should produce smaller changes in the observed coupling constants than those induced by a strong acid. To test this hypothesis, the molar quantities of trifluoroacetic, trichloroacetic and acetic acid were added to a chloroform solution of 20 and the n.m.r. spectra measured. The observed n.m.r. parameters are shown in Table 11.

TABLE 11

N.m.r. parameters (100 MHz) of 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20) in chloroform^a

	H-1'	J _{1',2'}	H-2'	J _{2',3'}	H-3'	J _{3',4'}	H-4'	J _{4',5'}
Acid	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)
Acetic Acid	3.87(d)	4.9	4.65(q)	9.6	4.41(q)	8.2	4.87(q)	9.6
Trichloro- acetic acid	3.67(d)	3.6	-	-	-	-	-	-
Trifluoro- acetic acid	3.71(d)	3.4	-	-	-	$\sim$ 5.6	4.94(m)	-

^aOne mole of various acids added per mole of 20.

From these results it may be interpreted that the higher the dissociation constant of the acid, the greater is the extent of protonation, and larger the contribution of 1C_4 conformation to the ${}^4C_1 \rightleftharpoons {}^1C_4$ equilibrium.

The fact that glucopyranosyl imidazole 20 did not decompose in solutions containing TFA or other acids was demonstrated by its recovery in near quantitative yield, after washing the acidic solution (chloroform) with a saturated solution of sodium bicarbonate. The n.m.r. spectrum of the recovered product was identical with that of the original α -*N*-glucoside (20).

N-Methylation of 20 should also result in a quaternized aglycon, and the n.m.r. parameters for the pyranose ring protons of this compound are expected to be similar to the *N*-protonated 20. *N*-Methylation of 20 gave 3-methyl-1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazolium iodide (44), the n.m.r. parameters of which are shown in Table 12 (Fig. 8).

TABLE 12

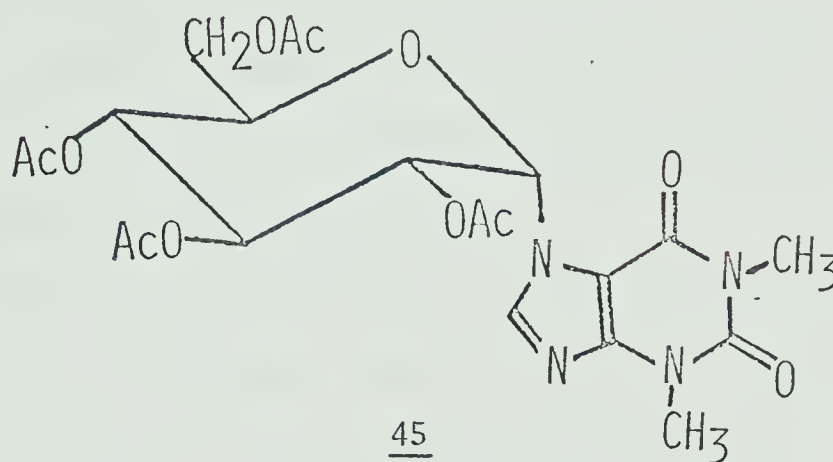
N.m.r. parameters (100 MHz) of 3-methyl-1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazolium iodide (44)

	H-1'	$J_{1',2'}$	H-2'	$J_{2',3'}$	H-3'	$J_{3',4'}$	H-4'	$J_{4',5'}$	$\overset{\oplus}{N}-CH_3$
Solvent	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)
CDCl ₃	3.32	3.7	4.51	6.7	4.72	5.3	4.96	~6.5	5.89
D ₂ O	3.07	3.8	-	-	-	-	-	-	5.60

The various coupling constants observed for 44 (Table 12) are of the

same order as previously observed when one mole of TFA was added to a mole of 20 in chloroform, thus supporting the conformational interpretation already proposed.

Onodera and coworkers (67) observed 2.5 Hz for $J_{1',2'}$ and 5.0 Hz for $J_{2',3'}$ for 7-(tetra-*O*-acetyl- α -D-glucopyranosyl)-theophylline (45) and explained that the compound showed reverse anomeric effect.

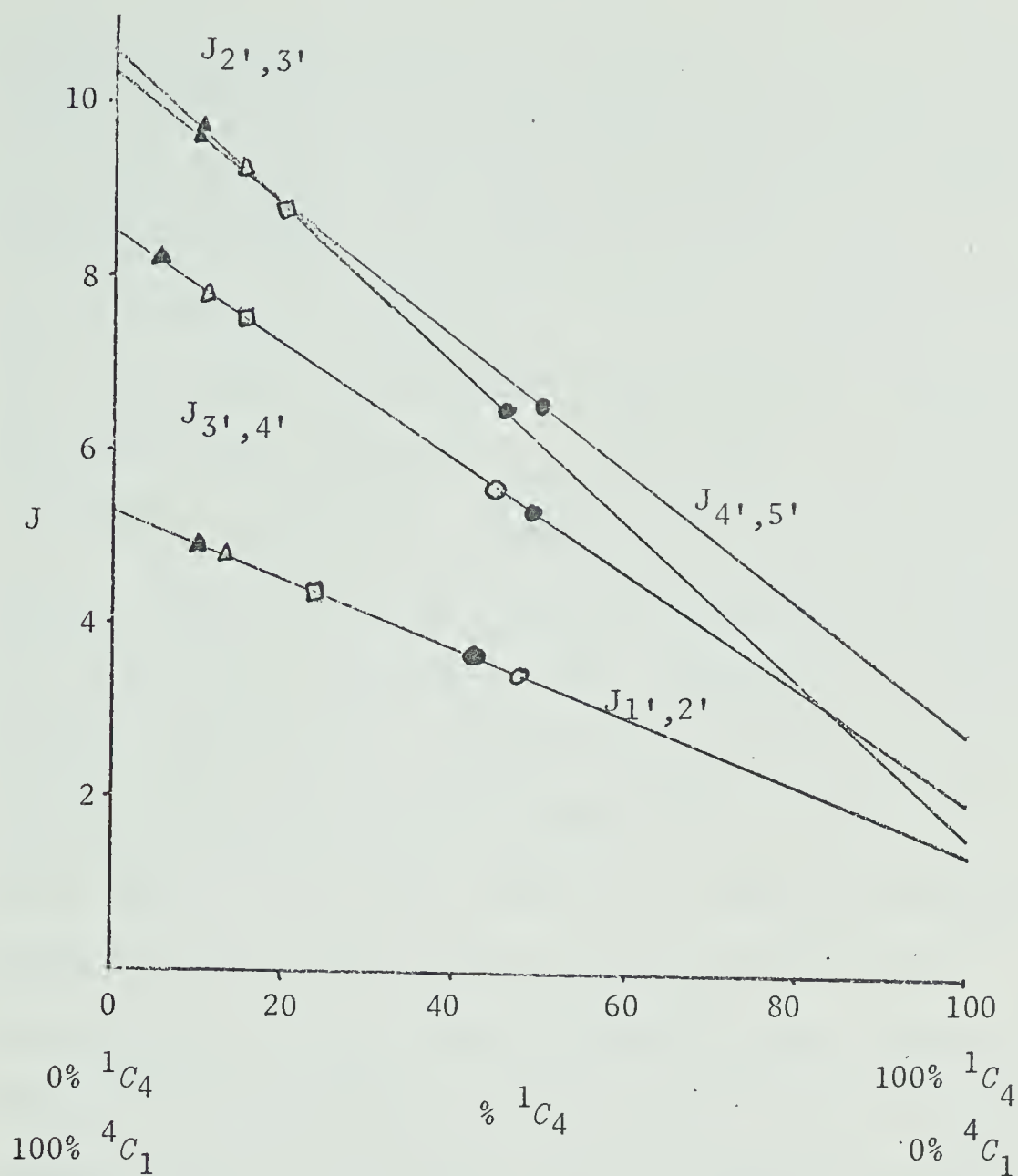


Since the nitrogen atom of the heterocyclic base is not quaternized to impart a positive charge to the aglycon, the reverse anomeric effect in this molecule is considered to arise from the conjugation of the lone-pair electrons of the anomeric nitrogen atom with the carbonyl group which undoubtedly imparts a positive charge. It is important to note that the coupling constant $J_{2',3'} = 5.0$ Hz obtained in this study cannot be accounted for by postulating the presence of a 4C_1 or 1C_4 conformation. Although these workers did not offer an explanation for this discrepancy the answer may well lie in the presence of ${}^4C_1 \rightleftharpoons {}^1C_4$ conformational equilibrium.

The observed coupling constants $J_{1',2'}$; $J_{2',3'}$; $J_{3',4'}$ and $J_{4',5'}$ for the pyranose ring protons should be a measure of the position

of the ${}^4C_1 \rightleftharpoons {}^1C_4$ equilibrium, if indeed there was such an equilibrium. Since the coupling constants for the pyranose ring protons of the unprotonated 20 in the 4C_1 conformation were known, it was thought that the existence of a ${}^4C_1 \rightleftharpoons {}^1C_4$ equilibrium for the protonated 18 could be evaluated on a somewhat quantitative basis, if the 1C_4 conformation of the molecule was assumed to have the following coupling constants: $J_{1',2'} = 1.4$; $J_{2',3'} = 1.6$; $J_{3',4'} = 2.0$ and $J_{4',5'} = 2.8$ Hz. Since these coupling constants represent only a $\pm 5^\circ$ variation in the dihedral angles between vicinal ring hydrogens in an ideal 1C_4 conformation, the above assumption seems justified.

The ${}^4C_1 \rightleftharpoons {}^1C_4$ conformational equilibrium for the *N*-protonated or *N*-methylated glucopyranosyl imidazoles may be examined on a quantitative basis as follows. If the compound existed solely in 4C_1 conformation, then the coupling constants $J_{2',3'}$, $J_{3',4'}$ and $J_{4',5'}$ should be in the region of 8-11 Hz (5,6), and this indeed has been found to be true for 20 (Table 9). On the other hand, 1C_4 conformation would have $H_{2'}$, $H_{3'}$, $H_{4'}$ and $H_{5'}$ in a *gauche* relationship, i.e., $J_{2',3'}$, $J_{3',4'}$, $J_{4',5'}$ being approximated to 1-4 Hz (5,6). It has already been demonstrated (page 99), that the proposed ${}^4C_1 \rightleftharpoons {}^1C_4$ equilibrium depends on the extent of protonation of the aglycon in 20, and consequently on the concentration and strength of the protonating acid. Since the experimentally obtained coupling constants represent the time averaged-equilibrium population of the two conformations, from this data the equilibrium constant with respect to each of the conformers may be calculated. As shown in Diagram 6, this may be achieved by plotting the values of the observed coupling constants, against an equilibrium



Diag. 6. Equilibrium composition of 1C_4 conformation vs. coupling constants of *N*-protonated or methylated 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole

- Δ 20 in CHCl_3 containing 0.25 molar equivalent of TFA
- $\square$ 20 in CHCl_3 containing 0.50 molar equivalent of TFA
- $\circ$ 20 in CHCl_3 containing 1.0 molar equivalent of TFA
- $\blacktriangle$ 20 in CHCl_3 containing 1.0 molar equivalent of CH_3COOH
- $\bullet$ 44 in D_2O

composition arrived at by considering that for $J_{1',2'}$, $J_{2',3'}$, $J_{3',4'}$ and $J_{4',5'}$ a value of 5.3, 10.5, 8.5 and 10.3 Hz, respectively, the equilibrium composition is 100% 4C_1 and 0% 1C_4 and for a value of 1.4, 1.6, 2.0 and 2.8 Hz, respectively, this composition is 0% 4C_1 and 100% 1C_4 . At a partial protonation of 20, effected by the addition of 0.25 mole of TFA, the observed $J_{1',2'}$ corresponds to an equilibrium containing 12% 1C_4 conformation. Similarly the other coupling constants, $J_{2',3'}$, $J_{3',4'}$ and $J_{4',5'}$ indicate this equilibrium concentration to be 14, 11 and 14%, respectively. This represents an average of $13\% \pm 2\%$ 1C_4 content in the mixture. Addition of 0.5 mole of TFA to a chloroform solution of 20 increased the amount of 1C_4 content to 19% (Diagram 6), the variation in this case being $\pm 3\%$. When the protonation of 20 is carried out by one mole of TFA or 20 is *N*-methylated, the equilibrium concentration of 1C_4 conformation should in both cases be the same. In the case of protonated 20 with one mole of TFA, the 1C_4 conformation content is 45%. On the other hand the coupling constants obtained for *N*-methylated glucoside 44 showed a variation of $\pm 5\%$ from the value of 45% as 1C_4 content. This margin of error is still well within the experimental limits of error, and does not constitute a serious threat to the main line of argument. The quantitative treatment presented above together with the preceding qualitative discussion may be considered to provide sufficient evidence supporting the existence of ${}^4C_1 \rightleftharpoons {}^1C_4$ conformational equilibrium for the *N*-protonated or methylated glucopyranosyl imidazoles.

Since the distribution of electrical charges tend to favor the equatorial orientation of the aglycon when it carries a positive charge, one would expect no conformational change

when a N - β -D-glucopyranoside is protonated or N -methylated. The n.m.r. spectrum of 1-(tetra- O -acetyl- β -D-glucopyranosyl)-imidazole (21), reproduced in Fig. 9, showed the same chemical shift (τ 4.72) for the four pyranose ring protons, and was thus not conducive to an analysis giving the parameters required. The β -D-configuration of 21 has already been established earlier (p. 53). On treatment of 21 in deuteriochloroform with one molar equivalent of TFA, the $H_{1'}$ resonance appeared at τ 4.12 as a doublet with a spacing of 8.3 Hz (Fig. 10) thus indicating a torsional angle close to 180° for $H_{1'}$ and $H_{2'}$. N -methylation of 21 gave 3-methyl-1-(tetra- O -acetyl- β -D-glucopyranosyl)-imidazolium iodide (46), the n.m.r. spectrum of which is reproduced in Fig. 11 and the parameters presented in Table 13.

TABLE 13

N.m.r. parameters (100 MHz) of 3-methyl-1-(tetra- O -acetyl- β -D-glucopyranosyl)-imidazolium iodide (46)

Solvent	$H_{1'}$ (τ)	$J_{1',2'}$ Hz	N^+-CH_3 (τ)
CDCl_3	3.50(d)	8.5	5.88
D_2O	3.54(m)	~ 8.6	5.62

$J_{1',2'}$ observed for 46 in both the solvents again indicated a torsional angle close to 180° for $H_{1'}$ and $H_{2'}$. These results are as expected for no conformational change on protonation or N -methylation of the β - N -glucoside 21.



Fig. 9. N.m.r. spectrum (100 MHz) of 1-(tetra-*O*-acetyl-β-D-glucopyranosyl)-imidazole (21) in deuteriochloroform.

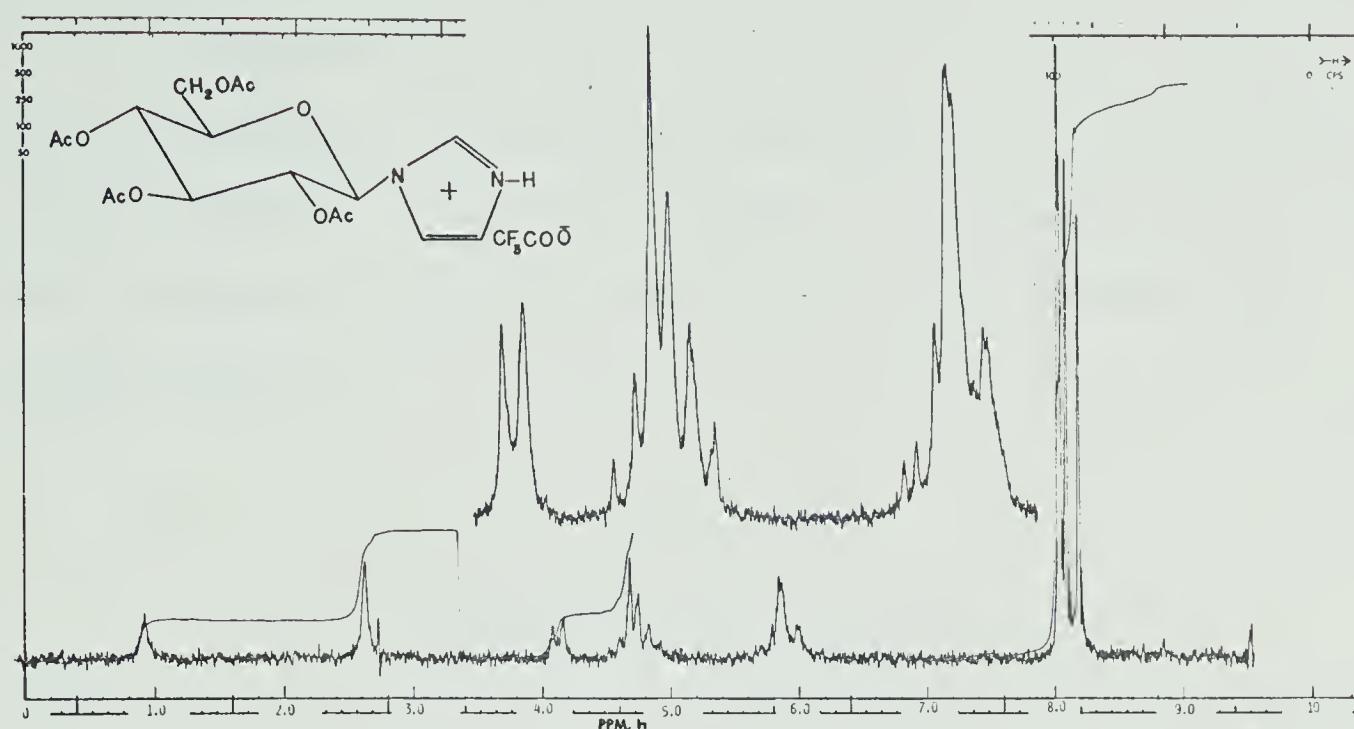


Fig. 10. N.m.r. spectrum (100 MHz) of 1-(tetra-*O*-acetyl-β-D-glucopyranosyl)-imidazole (21) in chloroform containing one molar equivalent of TFA. Inset, sweep width 500 Hz.

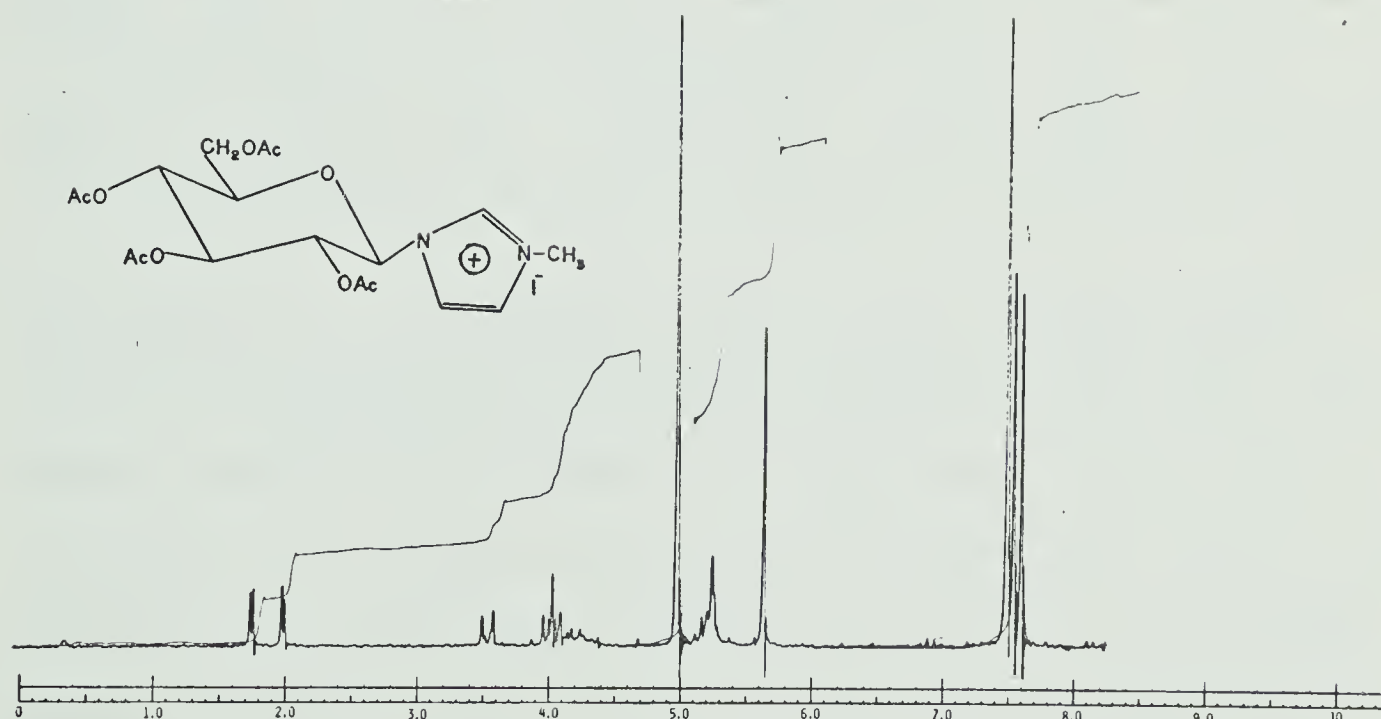


Fig. 11. N.m.r. spectrum (100 MHz) of 3-methyl-1-(tetra-*O*-acetyl-β-D-glucopyranosyl)-imidazolium iodide (46) in deuterium oxide.

Although the n.m.r. spectrum of 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32), in deuteriochloroform or 1,2-dichloroethane, was not amenable to a first order analysis, in acetone- d_6 , Fig. 12 the n.m.r. spectrum was near first order and the n.m.r. parameters are listed in Table 14.

TABLE 14

N.m.r. parameters (100 MHz) of 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32)

Solvent	H-1'	J _{1',2'}	H-2'	J _{2',3'}	H-3'	J _{3',4'}	H-4'	J _{4',5'}
	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)
Acetone- d_6	4.00(d)	5.2	4.25(q)	3.2	4.67(q)	6.8	4.82(q)	6.0
Pyri- dine- d_5	~ 3.8 (m)	-	~ 3.82 (m)	2.6	4.32(q)	6.9	4.48(q)	6.3
DMSO- d_6	4.05(d)	5.6	4.42(q)	3.4	4.80(q)	6.5	4.96(q)	6.2

The value of $J_{1',2'}$ in acetone- d_6 listed above is larger than that expected for an equatorial:equatorial orientation of $H_{1'}$ and $H_{2'}$, but smaller than that for the axial:axial orientation. A distortion or flattening of the pyranose ring from the 4C_1 conformation caused by the imidazole ring, would tend to increase the $H_{1'}-C_{1'}-C_{2'}-H_{2'}$ torsional angle, and would thus give a smaller J value than that expected for a true *gauche* relationship of these protons. On the other hand the values of $J_{3',4'}$ and $J_{4',5'}$ are smaller than those expected for the diaxial arrangement of vicinal protons. In order to draw a more realistic parallel with the behavior of *N*-glucopyranosyl imidazoles, an equilibrium

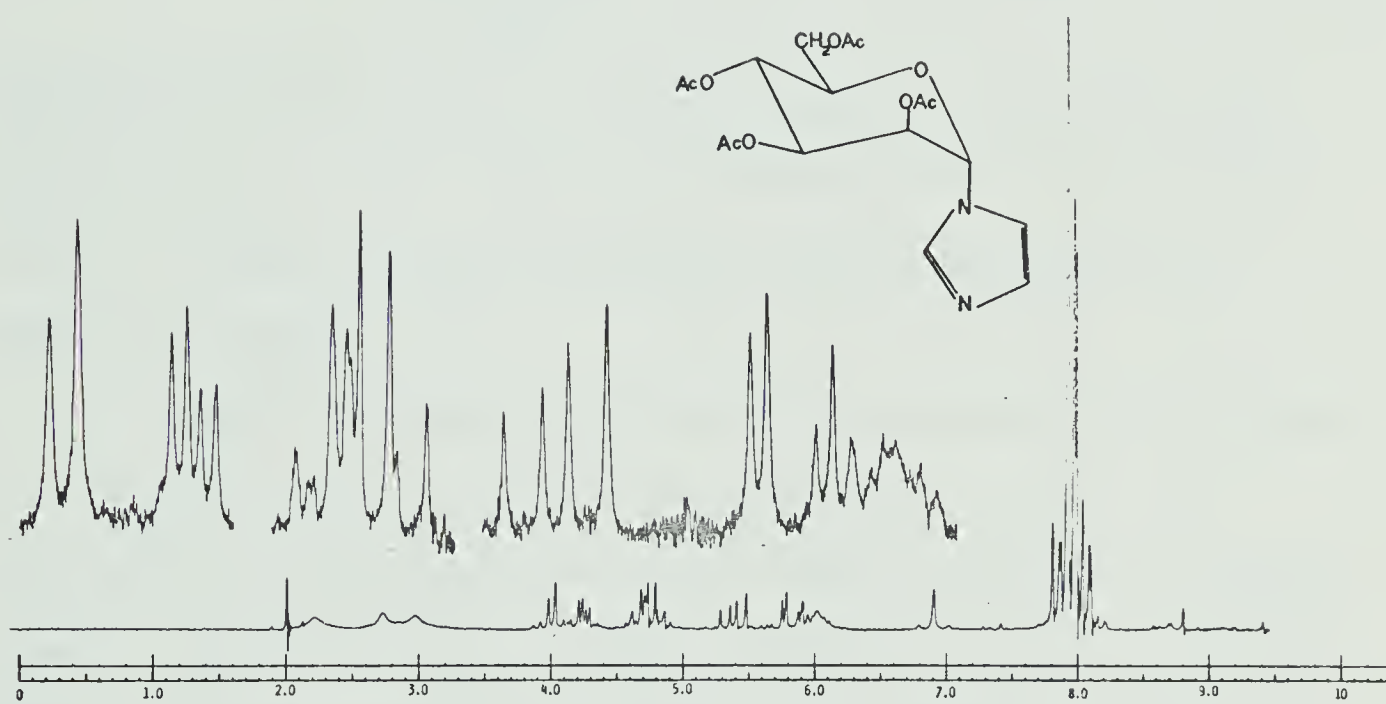
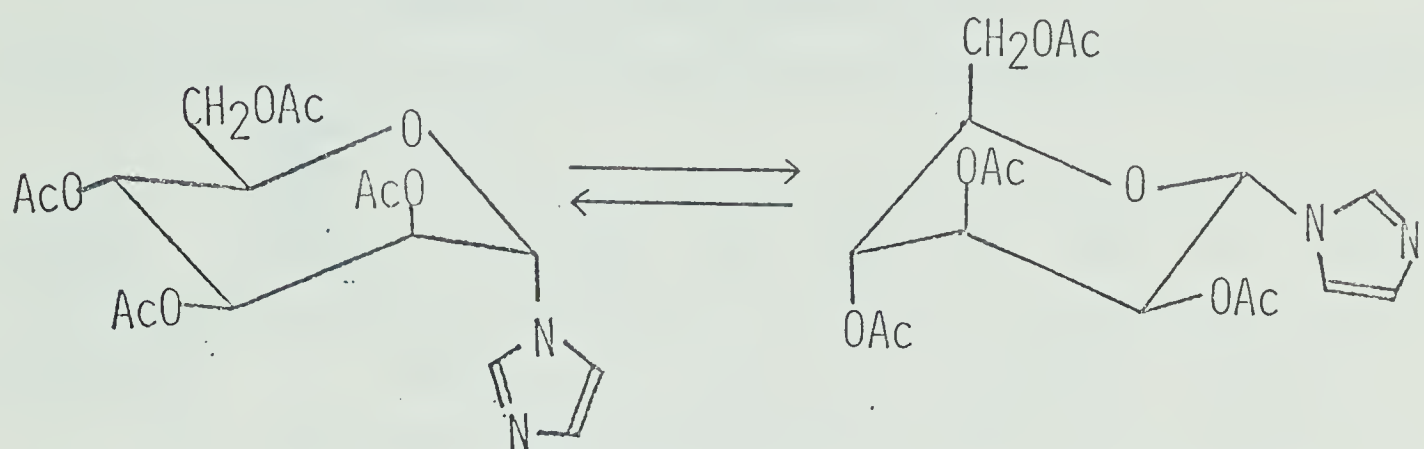


Fig. 12. N.m.r. spectrum (100 MHz) of 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32) in acetone-*d*₆. Inset, sweep width 250 Hz.

between 4C_1 and 1C_4 will again constitute the basic line of argument. One of the justifications for restricting the line of argument



to the consideration of chair conformations only has already been presented (page 102). The other justification will be found later on in the discussion, when this argument will be examined on a quantitative basis.

In order to examine the effect of protonation of the aglycon in 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32) on the conformation of the pyranose ring, the effect of addition of varying amounts of TFA to a solution of 32 in different solvents was studied. The n.m.r. data so obtained are summarised in Table 15. The value of $J_{1',2'}$ increased from 5.2 to 6.8 Hz in acetone- d_6 containing one mole of TFA per mole of 32. This value is still significantly smaller than that expected for an axial:axial arrangement of protons at C_1' and C_2' for a 1C_4 conformation. Thus, it would appear that in the presence of one mole TFA per mole of 32, conformational equilibrium is displaced further towards 1C_4 conformation. This conclusion was substantiated by the observed $J_{3',4'}$ and $J_{4',5'}$ coupling constants, and is consistent with the reverse anomeric effect.

TABLE 15

N.m.r. parameters (100 MHz) of 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32) in different solvents containing varying amounts of TFA

Solvent	Mole of TFA/ mole of <u>31</u>	H-1' (τ)	J _{1',2'} (Hz)	H-2' (τ)	J _{2',3'} (Hz)	H-3' (τ)	J _{3',4'} (Hz)	H-4' (τ)	J _{4',5'} (Hz)
Acetone-d ₆	0	4.00(d)	5.2	4.25(q)	3.2	4.67(q)	6.8	4.82(q)	6.0
	1.0	3.61(d)	6.8	4.27(q)	3.2	4.52(q)	5.3	4.78(q)	4.7
Deuterio- chloroform	1.0	3.84(d)	7.7	~4.50(m)	~3.2	~4.6(m)	4.7	4.94(q)	-
1,2-Dichloro- ethane	0.5	4.08(d)	6.3	4.41(q)	3.2	4.69(q)	6.0	4.90(q)	4.7
	1.0	3.96(d)	7.4	4.53(q)	3.1	4.66(q)	5.0	4.97(q)	3.2

The data obtained from the n.m.r. spectrum of 32 in deuteriochloroform in the presence of 1 mole of TFA (Fig. 13), are recorded in Table 15. The J_{1',2'} value of 7.7 Hz indicates nearly axial-axial arrangement for H_{1'} and H_{2'}, and therefore a large ¹C₄ equilibrium population. As previously observed in the case of the *gluco*-analog 20, one would expect a relationship between the observed coupling constants and the amount of acid added to protonate the imidazole ring. In other words, the addition of one half mole of TFA per mole of 32 should produce smaller changes in the observed coupling constants than the addition of one mole of TFA. Indeed, the addition of one half a mole of TFA to a solution of 32 in 1,2-dichloroethane gave

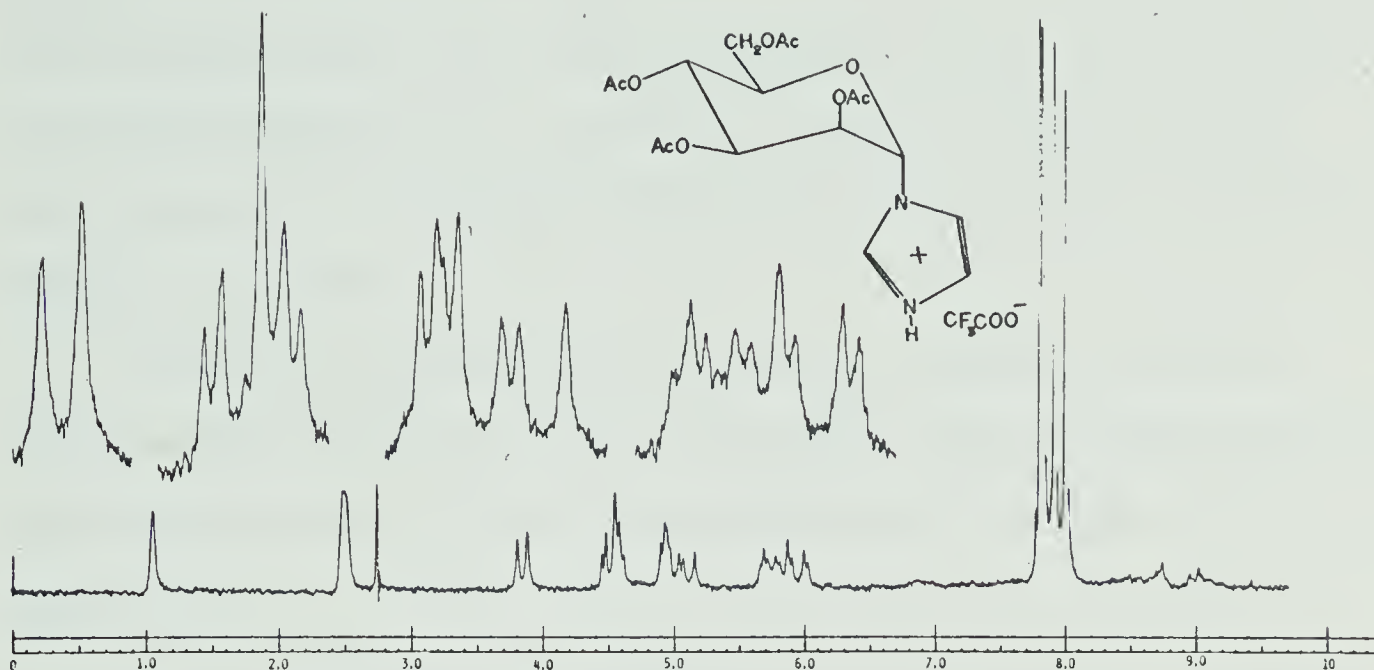


Fig. 13. N.m.r. spectrum (100 MHz) of 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32) in deuteriochloroform containing one molar equivalent of TFA. Inset, sweep width 250 Hz.

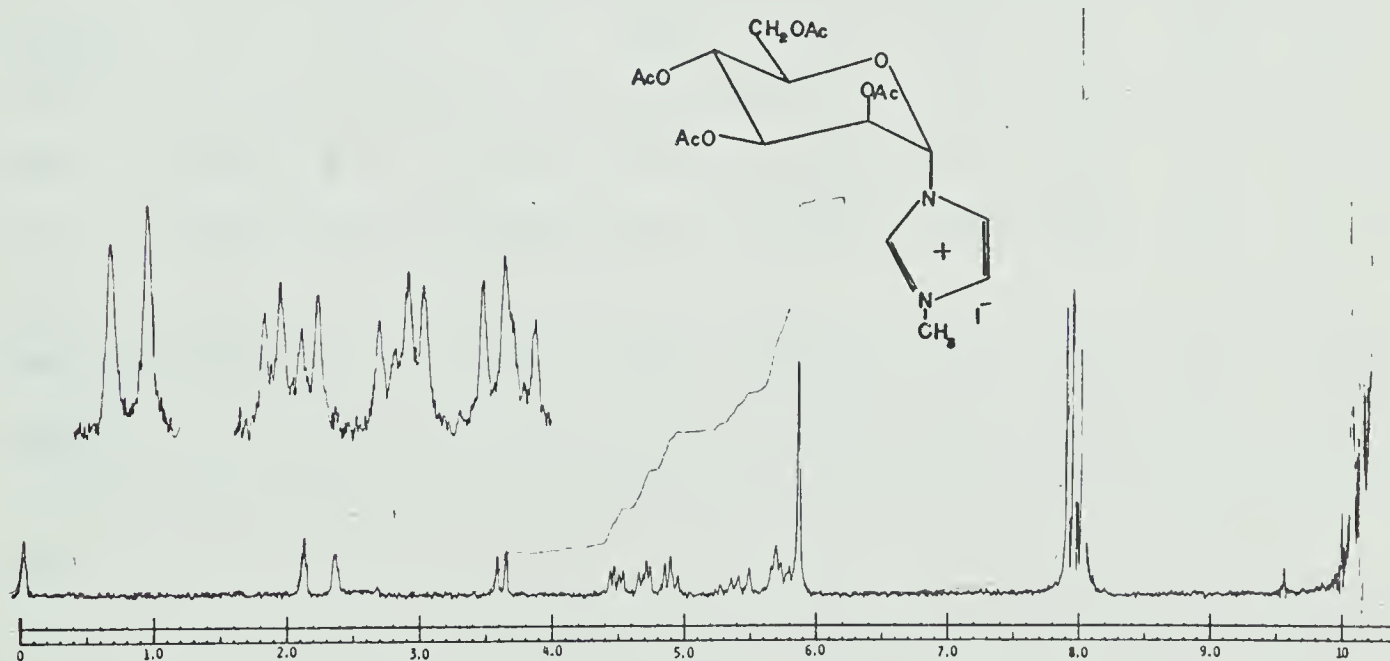


Fig. 14. N.m.r. spectrum (100 MHz) of 3-methyl-1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazolium iodide (47) in deuteriochloroform. Inset, sweep width 250 Hz.

$J_{1',2'}$ as 6.3 Hz, whereas, this value increased to 7.4 Hz when one mole TFA was added (Table 15). The corresponding changes in the value of the coupling constants $J_{3',4'}$ and $J_{4',5'}$, further substantiated the above mentioned relationship between the coupling constants and the amount of acid added.

The n.m.r. spectral data obtained for 3-methyl-1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazolium iodide (47), are summarised in Table 16 and the spectrum in deuteriochloroform is reproduced in Fig. 14.

TABLE 16

N.m.r. parameters (100 MHz) of 3-methyl-1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazolium iodide (47)

Solvent	H-1' (τ)	$J_{1',2'}$ (Hz)	H-2' (τ)	$J_{2',3'}$ (Hz)	H-3' (τ)	$J_{3',4'}$ (Hz)	H-4' (τ)	$J_{4',5'}$ (Hz)	$\text{N-CH}_3^{\oplus}$ (τ)
CDCl_3	3.62(d)	6.8	4.49(q)	3.0	4.70(q)	5.5	4.90	4.5	5.87
D_2O	3.28(d)	6.0	3.82(q)	3.0	4.10(q)	6.5	4.29	5.5	5.60
Ace- tone- d_6	3.41(d)	6.5	4.36(q)	3.0	4.61(q)	6.0	4.81	4.5	5.88
$\text{DMSO}-d_6$	3.81(d)	6.0	4.43(q)	3.5	4.73(q)	6.2	4.94	5.7	6.18

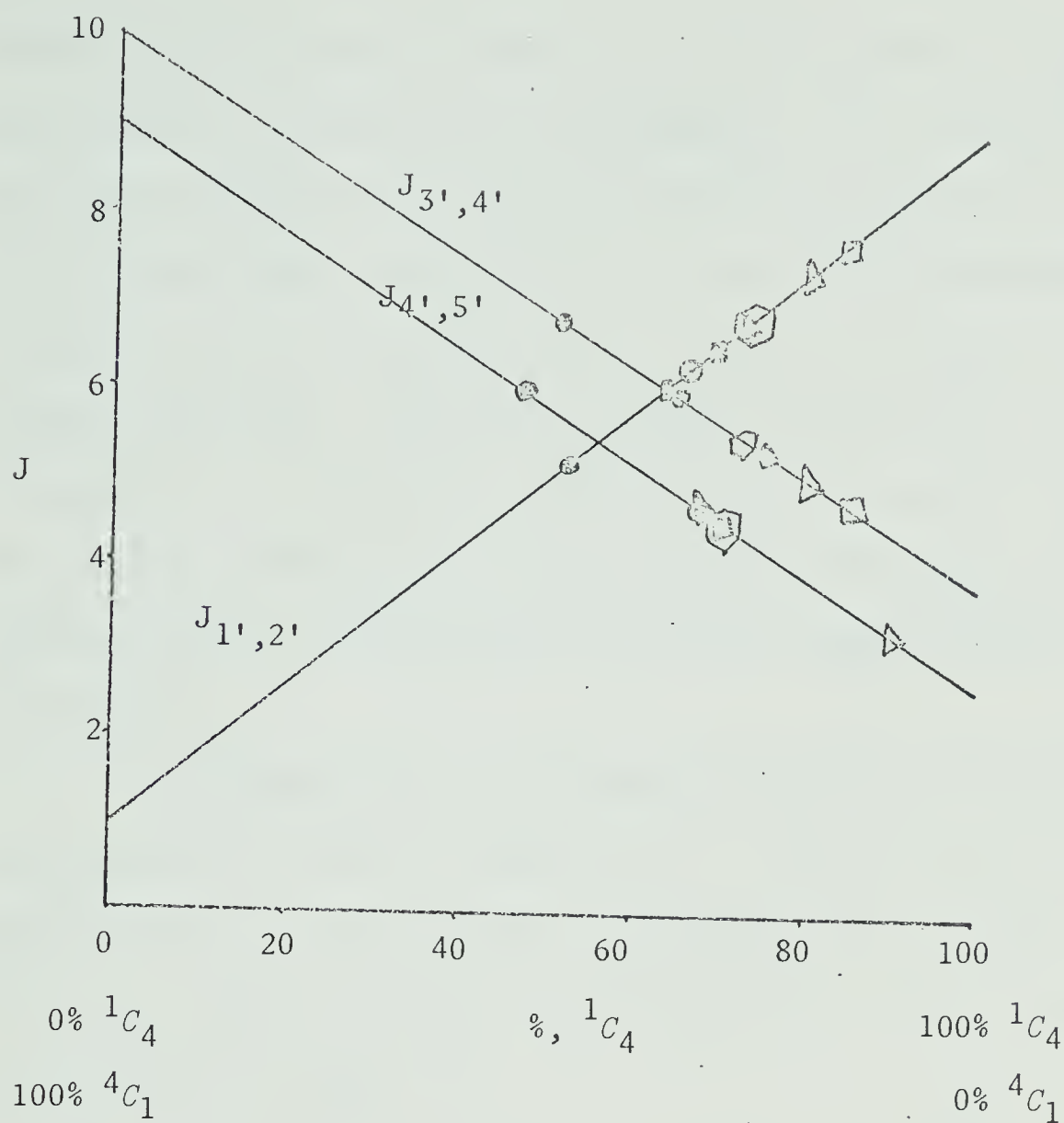
The coupling constants for the ring protons of 47 are of the same magnitude as those obtained on protonation of 32 with 1 mole of TFA. This suggests an equilibrium between the 4C_1 and 1C_4 conformation, and the coupling constants observed are of intermediate values between those expected for either of these conformations.

Onodera and coworkers (66) observed the following coupling constants for 7-(tetra-*O*-acetyl- α -D-mannopyranosyl)-theophylline in deuteriochloroform: $J_{1',2'} = 8.7$, $J_{2',3'} = 3.3$, $J_{3',4'} = 3.7$ and $J_{4',5'} = 3.7$ Hz. These coupling constants, as the authors point out, strongly support the predominant presence of the 1C_4 conformation. The reason for this "conformational inversion" would be twofold; firstly, the conjugation in the aglycon could impart a partial positive charge on the nitrogen atom attached to $C_{1'}$, thus giving rise to a situation conducive to the reverse anomeric effect and secondly, the steric strain involved in accommodation of the bulky aglycon might be minimized when the pyranose ring is in the 1C_4 conformation.

In keeping with the quantitative analysis of the results already presented for the *gluco* configuration, a similar treatment of the corresponding *manno* case will be discussed. Unlike 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20), which is predominantly in the 4C_1 conformation, the corresponding 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole (32) exists in ${}^4C_1 \rightleftharpoons {}^1C_4$ equilibrium. This required the use of a model molecule such as tetra-*O*-acetyl- α -D-mannopyranosyl bromide existing in the 4C_1 conformation, to supply the necessary pyranose ring proton coupling constants for an α -D-mannopyranoside conformation. Since it was found, that in the case of 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (18) the presence of the hetero aglycon caused a local flattening of the pyranose ring, which resulted in a reduction of the dihedral angle (i.e., in this case $J_{1',2'}$ increased). The corresponding effect is assumed to take place in the case of 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole

(32), resulting in the reduction of the coupling constant $J_{1',2'}$. Thus, modifying $J_{1',2'}$ in tetra-*O*-acetyl- α -D-mannopyranosyl bromide from 1.6 to 1.0 Hz and leaving $J_{2',3'} = 3.0$, $J_{3',4'} = 10.0$, $J_{4',5'} = 9.4$ Hz in their original form (108) provided a workable standard for quantitative considerations of ${}^4C_1 \rightleftharpoons {}^1C_4$ equilibrium. This task was made more difficult by a lack of coupling constants for the ring protons of a suitable α -D-mannopyranoside existing in the 1C_4 conformation. In order to establish the ${}^4C_1 \rightleftharpoons {}^1C_4$ equilibrium for these compounds on a somewhat quantitative basis, the 1C_4 conformation of the molecule was assumed to have the following coupling constants: $J_{1',2'} = 9.0$, $J_{3',4'} = 3.8$ and $J_{4',5'} = 2.6$ Hz. These coupling constants represent a near 1C_4 conformation and the above assumption seems justified. It is relevant to point out at this stage that the *gauche* relationship between $H_{2'}$ and $H_{3'}$ does not change in going from 4C_1 to 1C_4 conformation of a α -D-mannopyranosyl imidazole, hence the absence of $J_{2',3'}$ from further considerations.

The ${}^4C_1 \rightleftharpoons {}^1C_4$ equilibrium already proposed for the α -*N*-mannoside 32 bearing the unprotonated aglycon can now be seen (Diag. 7) to be populated to an extent of 51% by the molecules in 1C_4 conformation when the solvent was acetone- d_6 . As in the case of α -*N*-glucoside 20, the protonation of the aglycon was observed to shift the equilibrium towards a position of higher population of 1C_4 conformation. It can clearly be seen from the graph that when protonation of 32 in acetone- d_6 was effected with one mole of TFA, the equilibrium content of 1C_4 conformation increased to 73%. An increase to 66% was observed on *N*-methylation of the aglycon of 31 in acetone- d_6 . Similar trend,



Diag. 7. Equilibrium composition of 1C_4 conformation vs. coupling constants of *N*-protonated or methylated 1-(tetra-*O*-acetyl- α -D-mannopyranosyl)-imidazole

- 32 in 1,2-dichloroethane containing 0.5 molar equivalent of TFA
- △ 32 in 1,2-dichloroethane containing 1.0 molar equivalent of TFA
- 32 in CDCl_3 containing 1.0 molar equivalent of TFA
- 32 in acetone- d_6
- ▲ 32 in acetone- d_6 containing 1.0 molar equivalent of TFA
- 47 in acetone- d_6
- ⬡ 47 in CDCl_3

amounting to the reverse anomeric effect, was observed on complete protonation or *N*-methylation of the aglycon in 32 in other solvents. Thus when imidazole ring in 32 was either protonated with one mole of TFA or *N*-methylated, the equilibrium content of 1C_4 conformation was found to be at its highest values of 84 and 73%, respectively, in deuteriochloroform. Although the equilibrium composition of 32 containing the unprotonated imidazole ring could not be obtained in deuteriochloroform because of the complexity of the n.m.r. spectrum, it would seem that in this solvent the reverse anomeric effect is most pronounced.

As already shown, the β -*N*-glucoside 21 did not undergo any conformational change on *N*-methylation. A similar behavior should be expected from 1-(tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazole (33). The n.m.r. spectrum of 33 is reproduced in Fig. 15 and the parameters are presented in Table 17.

TABLE 17

N.m.r. parameters (100 MHz) of 1-(tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazole (33)

	H-1'	$J_{1',2'}$	H-2'	$J_{2',3'}$
Solvent	(τ)	(Hz)	(τ)	(Hz)
Acetone- d_6	3.89(d)	1.0	4.50(q)	2.8
CDCl ₃	4.27(d)	1.2	4.46(q)	2.4

$J_{1',2'}$ of the order of 1 Hz is typical of β -D-mannopyranosyl

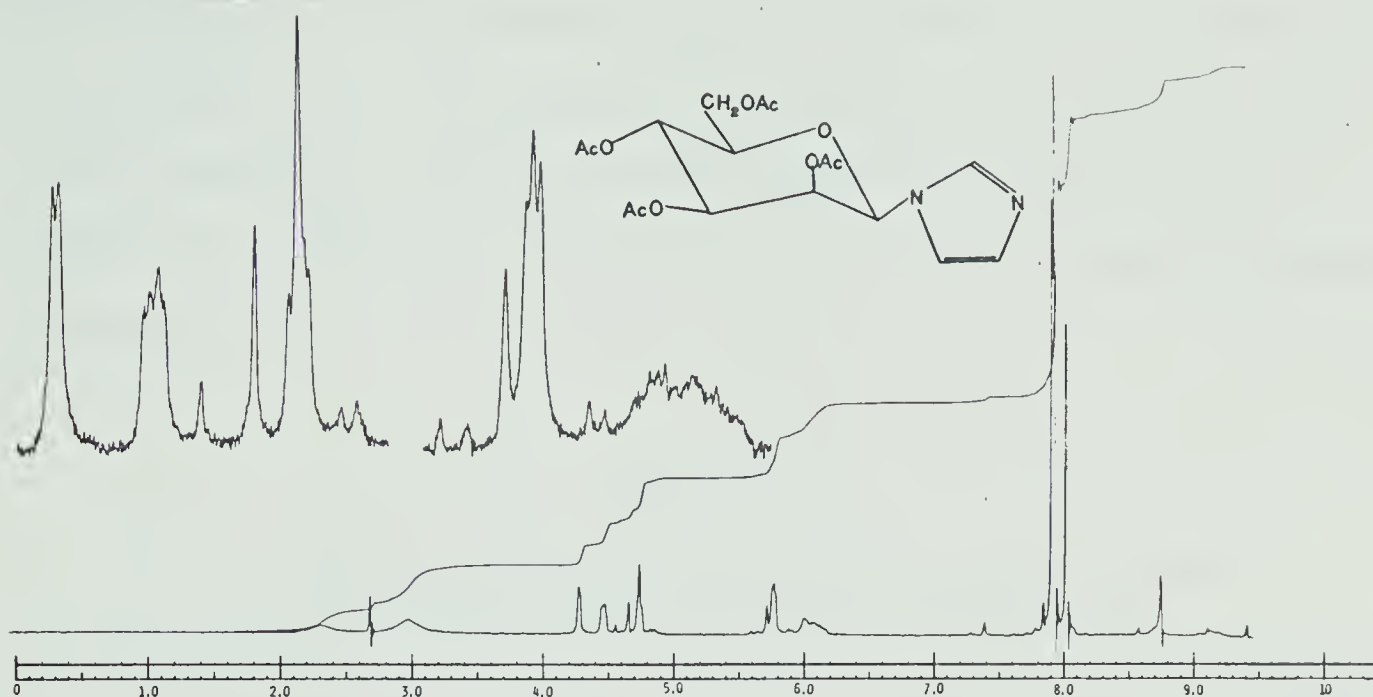


Fig. 15. N.m.r. spectrum (100 MHz) of 1-(tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazole (33) in deuteriochloroform. Inset, sweep width 250 Hz.

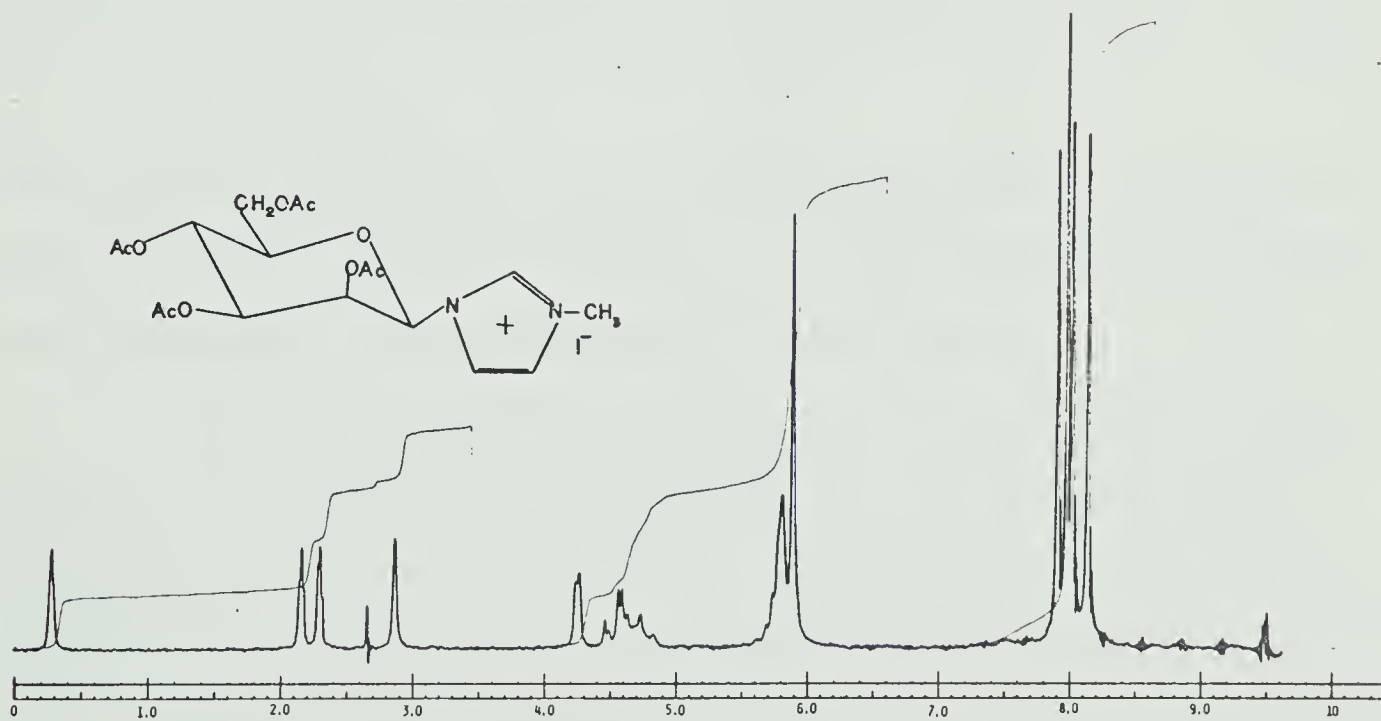


Fig. 16. N.m.r. spectrum (100 MHz) of 3-methyl-1-(tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazolium iodide (48) in deuteriochloroform.

derivatives (64). The observed $J_{1',2'}$ of the order of 1.0 Hz and 1.2 Hz does suggest the β -configuration at the anomeric center for 33. The n.m.r. spectrum of 3-methyl-1-(tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazolium iodide (48) is shown in Fig. 16 and the parameters presented in Table 18.

TABLE 18

N.m.r. parameters (100 MHz) of 3-methyl-1-tetra-*O*-acetyl- β -D-mannopyranosyl)-imidazolium iodide (48)

	H-1'	$J_{1',2'}$	H-2'	$J_{2',3'}$	N^+-CH_3
Solvent	(τ)	(Hz)	(τ)	(Hz)	(τ)
Acetone- d_6	3.02(d)	1.5	4.30(q)	2.7	5.94
CDCl_3	2.86(s)	<1	4.25	~ 2.0	5.89

By comparing the values of $J_{1',2'}$ for 33 and 48 (Tables 17 and 18), it may be concluded that there seems to be no conformational change when imidazole ring in the β -orientation is quaternized.

Studies of *O*-deacetylated *N*-glucosides were not very rewarding because of the difficulties in obtaining all of the required n.m.r. parameters. The n.m.r. spectrum of 1-(α -D-glucopyranosyl)-imidazole (49) is shown in Fig. 17 and the parameters presented in Table 19.

$J_{2',3'}$ values are only approximate because of the small chemical shift difference between H_2' , H_3' and H_4' . However, the results presented in Table 19 for 49 do suggest that 49 is present in the 4C_1 conformation with the imidazole ring occupying the axial orientation.

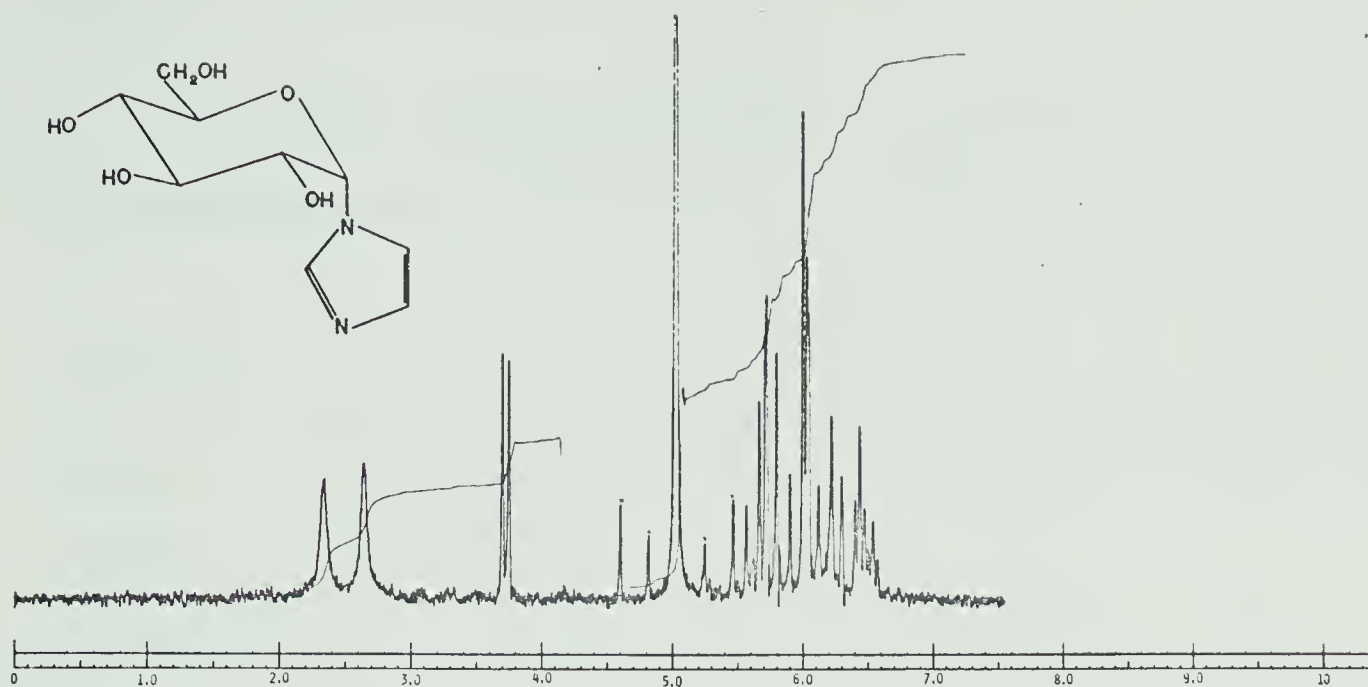


Fig. 17. N.m.r. spectrum (100 MHz) of 1-(α -D-glucopyranosyl)-imidazole (49) in deuterium oxide.

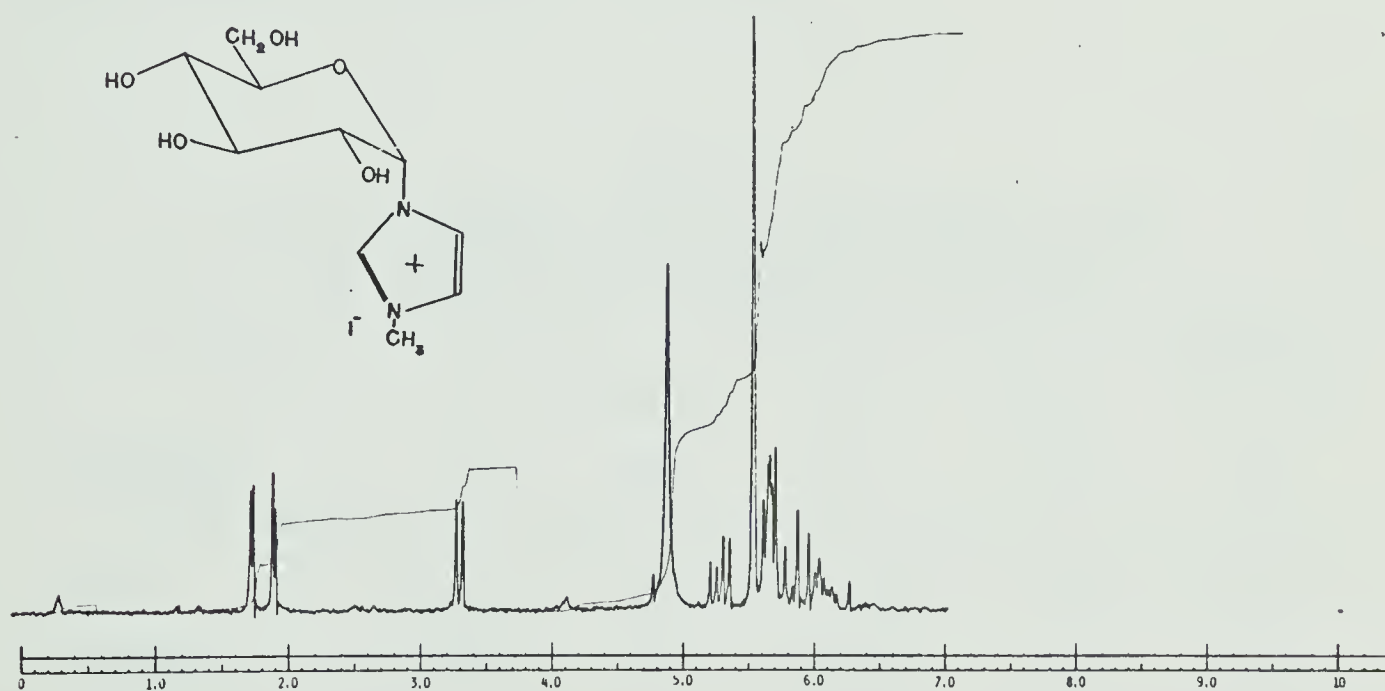


Fig. 18. N.m.r. spectrum (100 MHz) of 3-methyl-1-(α -D-glucopyranosyl)-imidazolium iodide (50) in deuterium oxide.

TABLE 19

N.m.r. parameters (100 MHz) of 1-(α -D-glucopyranosyl)-imidazole (49)

Solvent	H-1' (τ)	$J_{1',2'}$ (Hz)	H-2' (τ)	$J_{2',3'}$ (Hz)
D ₂ O	3.72(d)	4.8	$\sim$ 5.65(m)	$\sim$ 10
DMSO- <i>d</i> ₆	4.26(d)	4.7	-	-
MeOD- <i>d</i> ₄	3.92(d)	4.8	$\sim$ 5.90(m)	$\sim$ 10

3-Methyl-1-(α -D-glucopyranosyl)-imidazolium iodide (50) was obtained on *N*-methylation of 49 and its n.m.r. spectrum is reproduced in Fig. 18 and the parameters presented in Table 20.

TABLE 20

N.m.r. parameters (100 MHz) of 3-methyl-1-(α -D-glucopyranosyl)-imidazolium iodide (50)

Solvent	H-1' (τ)	$J_{1',2'}$ (Hz)	H-2' (τ)	$J_{2',3'}$ (Hz)	$\text{N}^{\oplus}\text{-CH}_3$ (τ)
D ₂ O	3.29(d)	5.0	5.27(q)	9.8	5.53
DMSO- <i>d</i> ₆	3.98(d)	5.0	6.20(q)	9.4	6.14
MeOD- <i>d</i> ₄	3.98(d)	4.5	$\sim$ 6.06(q)	$\sim$ 9.5	5.86

The coupling constants observed for 50 suggest no departure from the 4C_1 conformation. This is in contrast to the behavior of the fully

acetylated analogue of 50, i.e., 3-methyl-1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazolium iodide (44), which exhibits the reverse anomeric effect. However, similar contrasting observations may be shown from the work of Onodera and coworkers (67). On deacetylation of 7-(tetra-*O*-acetyl- α -D-glucopyranosyl)-theophylline (45), which exhibits the reverse anomeric effect, the resulting 7-(α -D-glucopyranosyl)-theophylline for which $J_{1',2'} = 6.0$, $J_{2',3'} = 7.0$ and $J_{3',4'} = 7.0$ Hz (obtained from signal half widths), in DMSO- d_6 , indicate the presence of predominantly 4C_1 conformation.

1-(β -D-glucopyranosyl)-imidazole (51) was obtained by *O*-deacetylation of 1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21). The n.m.r. spectrum of 51 reproduced in Fig. 19 exhibited a doublet at τ 4.25 for $H_{1'}$ absorption with a spacing of 8.5 Hz ($J_{1',2'}$) which indicated diaxial arrangement between $H_{1'}$ and $H_{2'}$. In the case of *N*-methylated compound, 3-methyl-1-(β -D-glucopyranosyl)-imidazolium iodide (52), $J_{1',2'}$ was estimated to be about 8.8 Hz (Fig. 20) which again indicates the diaxial arrangement for the vicinal protons $H_{1'}$ and $H_{2'}$. As expected, no conformational change is observed in the case of this β -anomer 52.

Examination of 1-(α -D-mannopyranosyl)-imidazole (53) furnished the n.m.r. parameters shown in Table 21. The n.m.r. spectrum of 53 is reproduced in Fig. 21.

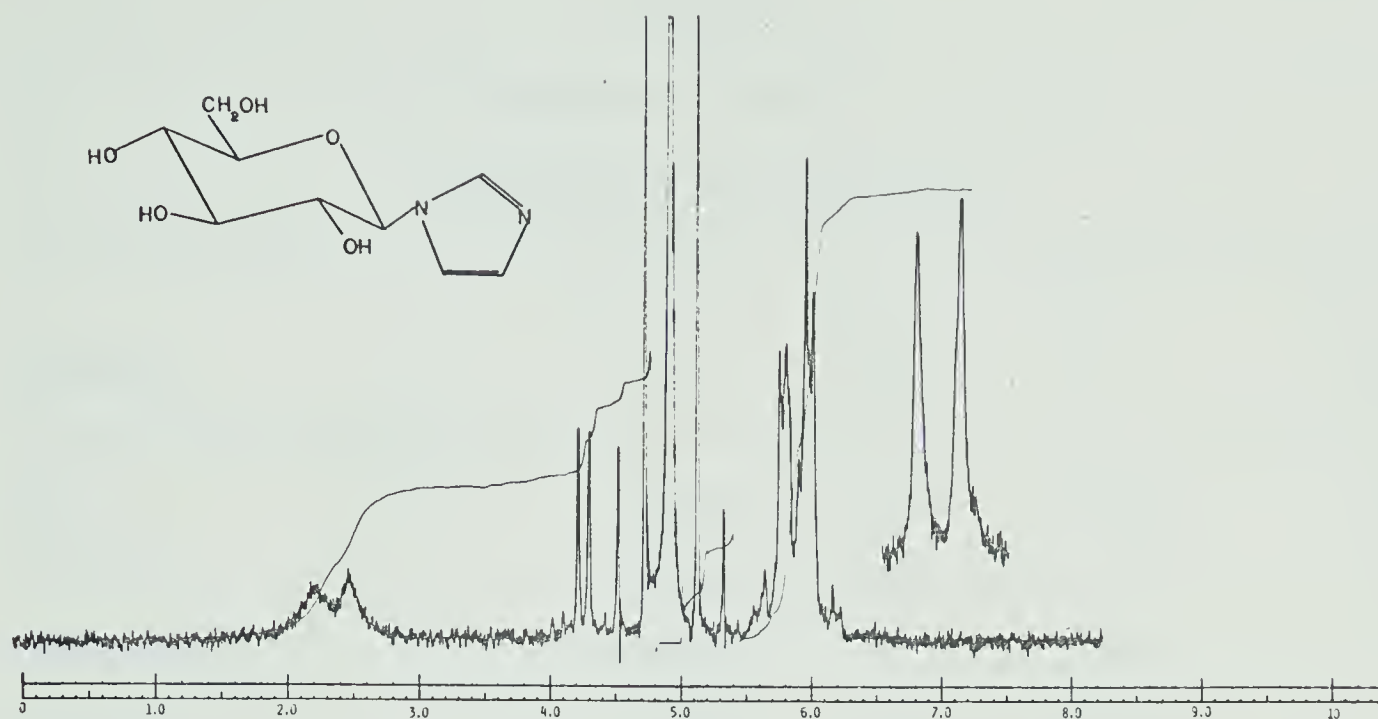


Fig. 19. N.m.r. spectrum (100 MHz) of 1-(β-D-glucopyranosyl)-imidazole (51) in deuterium oxide. Inset, sweep width 250 Hz.

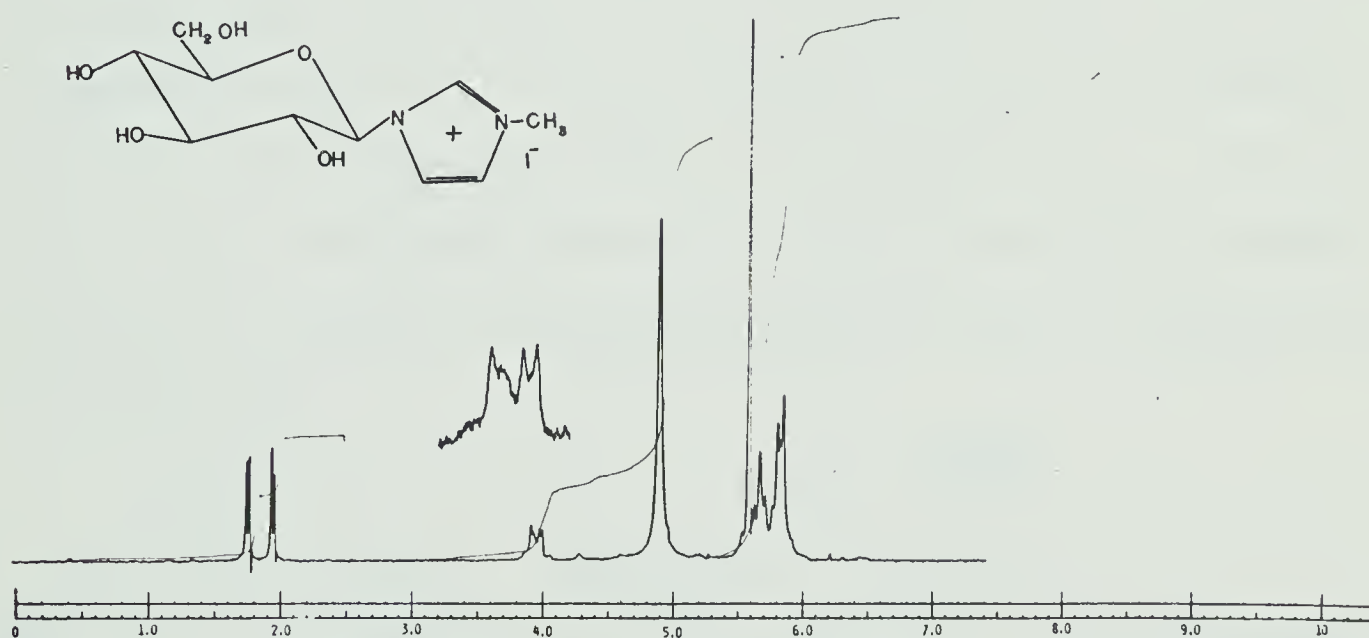


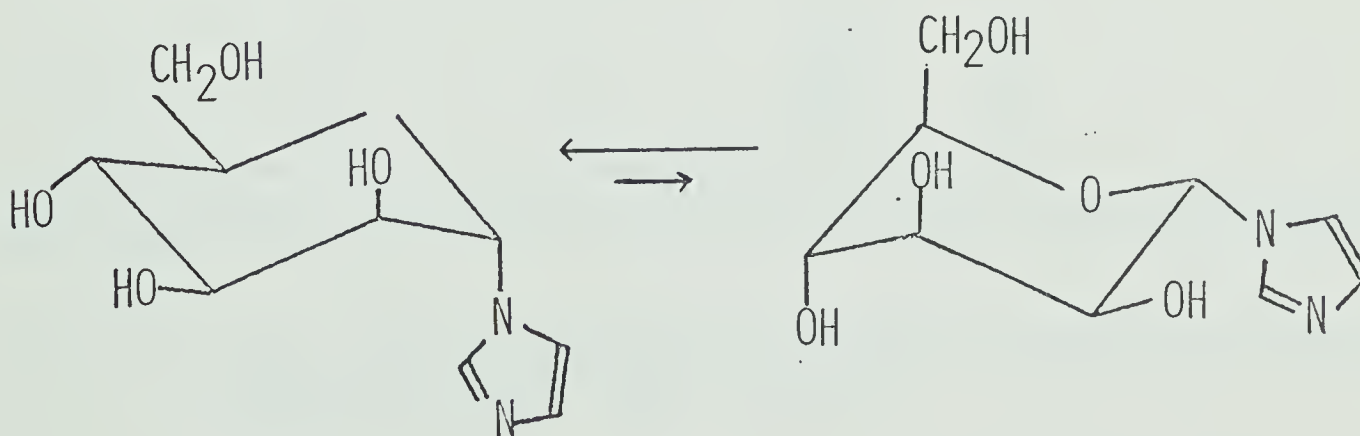
Fig. 20. N.m.r. spectrum (100 MHz) of 3-methyl-(β-D-glucopyranosyl)-imidazolium iodide (52) in deuterium oxide. Inset, sweep width 250 Hz.

TABLE 21

N.m.r. parameters (100 MHz) of 1-(α -D-mannopyranosyl)-imidazole (53)

Solvent	H-1' (τ)	$J_{1',2'}$ (Hz)	H-2' (τ)	$J_{2',3'}$ (Hz)
D ₂ O	3.76(d)	3.6	5.01(q)	2.7
MeOD- <i>d</i> ₄	3.84(d)	5.0	5.21(q)	2.7
Pyridine- <i>d</i> ₅	3.80(d)	5.1	5.06(q)	2.7
DMSO- <i>d</i> ₆	4.53(d)	6.3	5.93(q)	2.7

The above results strongly suggest a solvent effect on the conformational equilibrium c.f., variations in $J_{1',2'}$. This coupling constant is larger than would be expected had the compound been in the 4C_1 conformation only, i.e., vicinal diequatorial interaction between H_{1'} and H_{2'}. In the absence of other n.m.r. parameters ($J_{3',4'}$ and $J_{4',5'}$) and in view of the previous discussion of per-*O*-acetylated α -*N*-mannoside 32, there may be an equilibrium between 4C_1 and 1C_4 conformations as shown below:



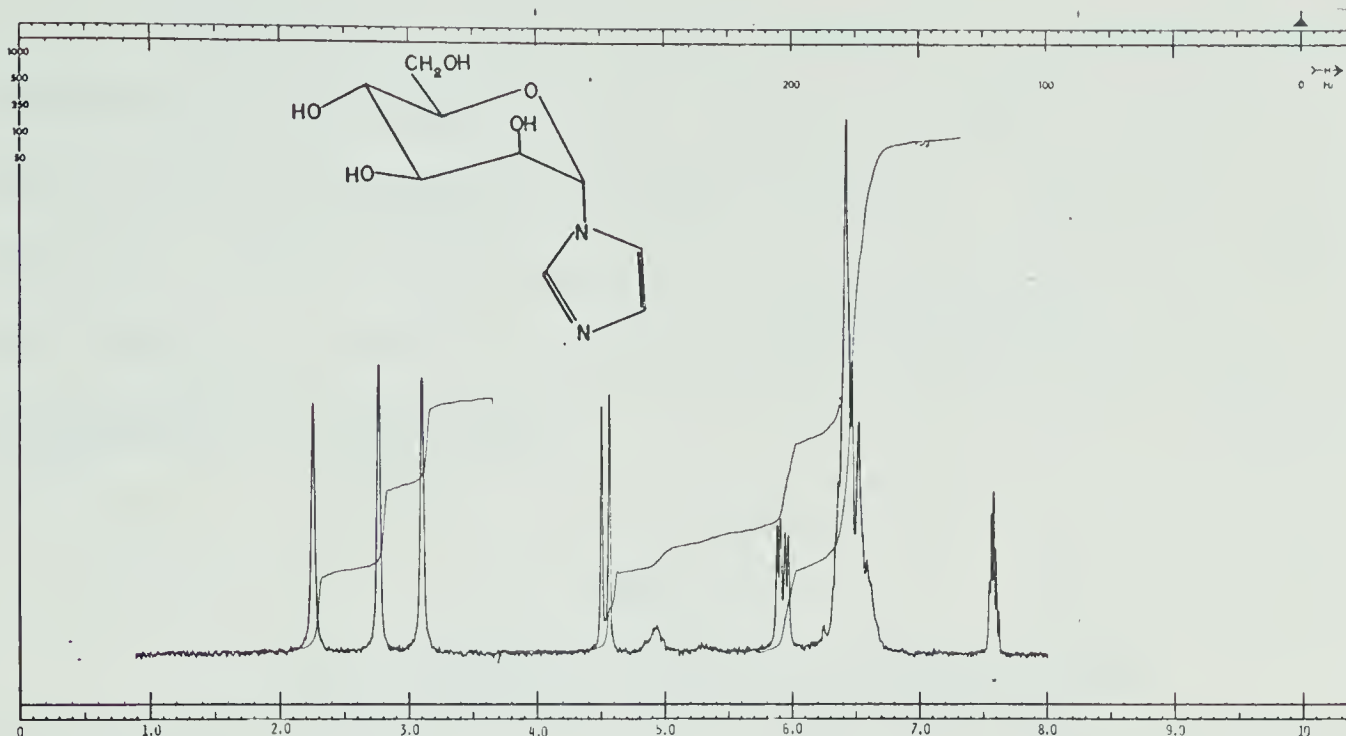


Fig. 21. N.m.r. spectrum (100 MHz) of 1-(α -D-mannopyranosyl)-imidazole (53) in DMSO- d_6 .

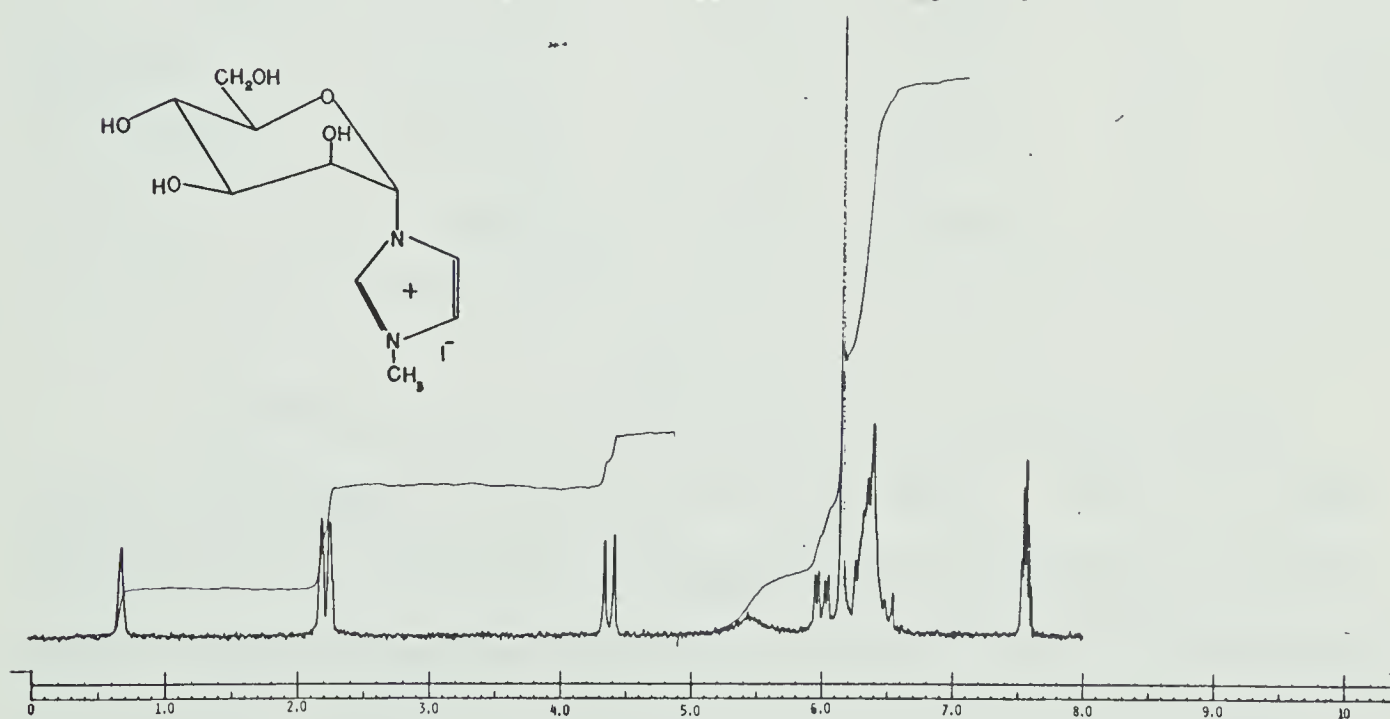


Fig. 22. N.m.r. spectrum (100 MHz) of 3-methyl-1-(α -D-mannopyranosyl)-imidazolium iodide (54) in DMSO- d_6 .

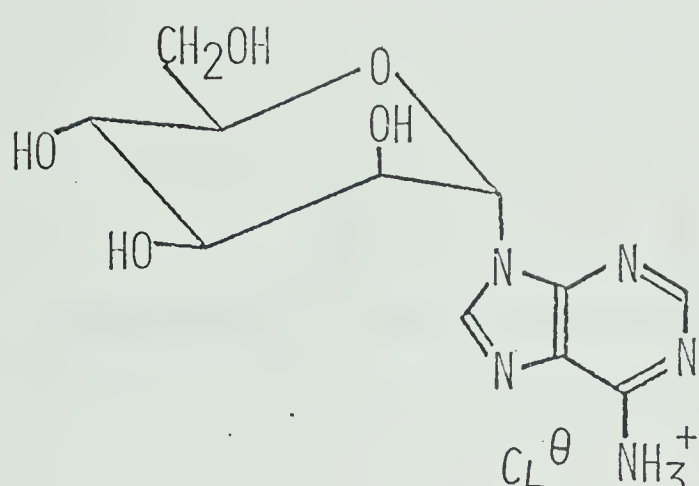
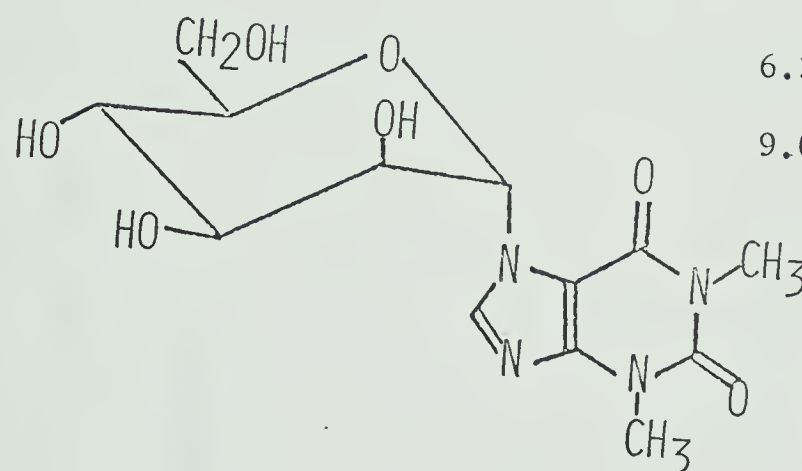
N-Methylation of 53 furnished 3-methyl-1-(α -D-mannopyranosyl)-imidazolium iodide (54), the n.m.r. spectrum of which is shown in Fig. 22 and the parameters presented in Table 22. Again only $J_{1',2'}$ and $J_{2',3'}$ could be readily obtained. It is clear from Table 22 that the effect of the solvent on the equilibrium between 4C_1 and 1C_4 conformation is still strong.

TABLE 22

N.m.r. parameters (100 MHz) of 3-methyl-1(α -D-mannopyranosyl)-imidazolium iodide (54)

Solvent	H-1'	$J_{1',2'}$	H-2'	$J_{2',3'}$	$\text{N-CH}_3^\oplus$
	(τ)	(Hz)	(τ)	(Hz)	(τ)
D ₂ O	3.62(d)	4.3	5.04(q)	2.3	5.64
MeOD- <i>d</i> ₄	4.24(d)	7.2	5.91(q)	2.8	6.09
Pyridine- <i>d</i> ₅	4.04(d)	6.9	5.50(q)	2.6	6.60
DMSO- <i>d</i> ₆	4.38(d)	7.5	6.00(q)	3.0	6.15

In DMSO-*d*₆, $J_{1',2'}$ observed being 7.5 Hz indicate nearly diaxial arrangement of vicinal protons H_{1'} and H_{2'}. This is a clear indication of a conformational change caused by the reverse anomeric effect, thus shifting the equilibrium from the 4C_1 to 1C_4 conformation as expected. Onodera and coworkers (66,67) reported the coupling constants for the following α -D-mannopyranosyl derivatives:

	Coupling Constants			Solvent
	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	
	6.0	3.0	-	D ₂ O
	8.3	3.0	3.2	DMSO- <i>d</i> ₆
	6.2	3.5	5.0	D ₂ O
	9.0	3.0	-	DMSO- <i>d</i> ₆

On the basis of these spacings, the authors suggested a 4C_1 and 1C_4 conformational equilibrium in D₂O for these compounds, whereas in DMSO-*d*₆ the presence of only 1C_4 conformation was suggested. The n.m.r. spectrum of 1-(β-D-mannopyranosyl)-imidazole (55) is shown in Fig. 23. $H_{1'}$ appeared at τ 3.94 as a doublet with a spacing of 1.3 Hz. $J_{1',2'}$ of this magnitude is typical of β-compounds in the D-mannose

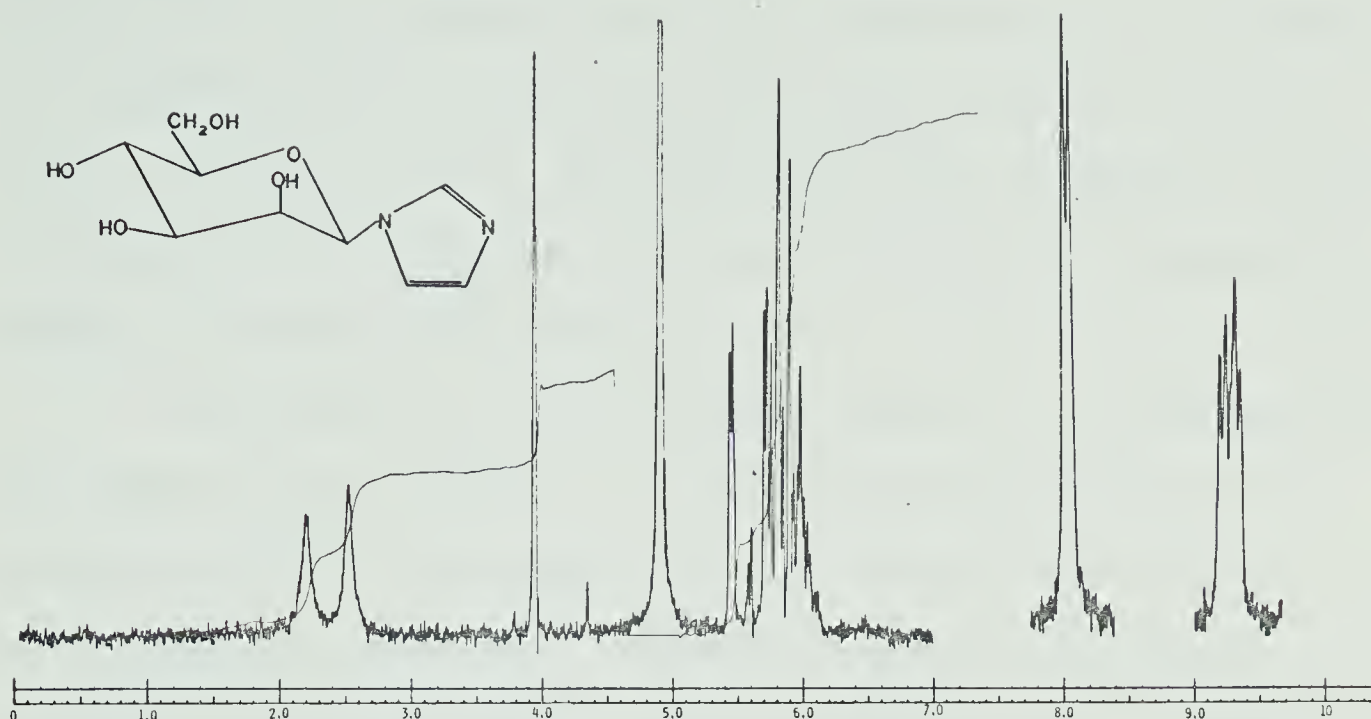


Fig. 23. N.m.r. spectrum (100 MHz) of 1-(β-D-mannopyranosyl)-imidazole (55) in deuterium oxide. Inset, sweep width 250 Hz.

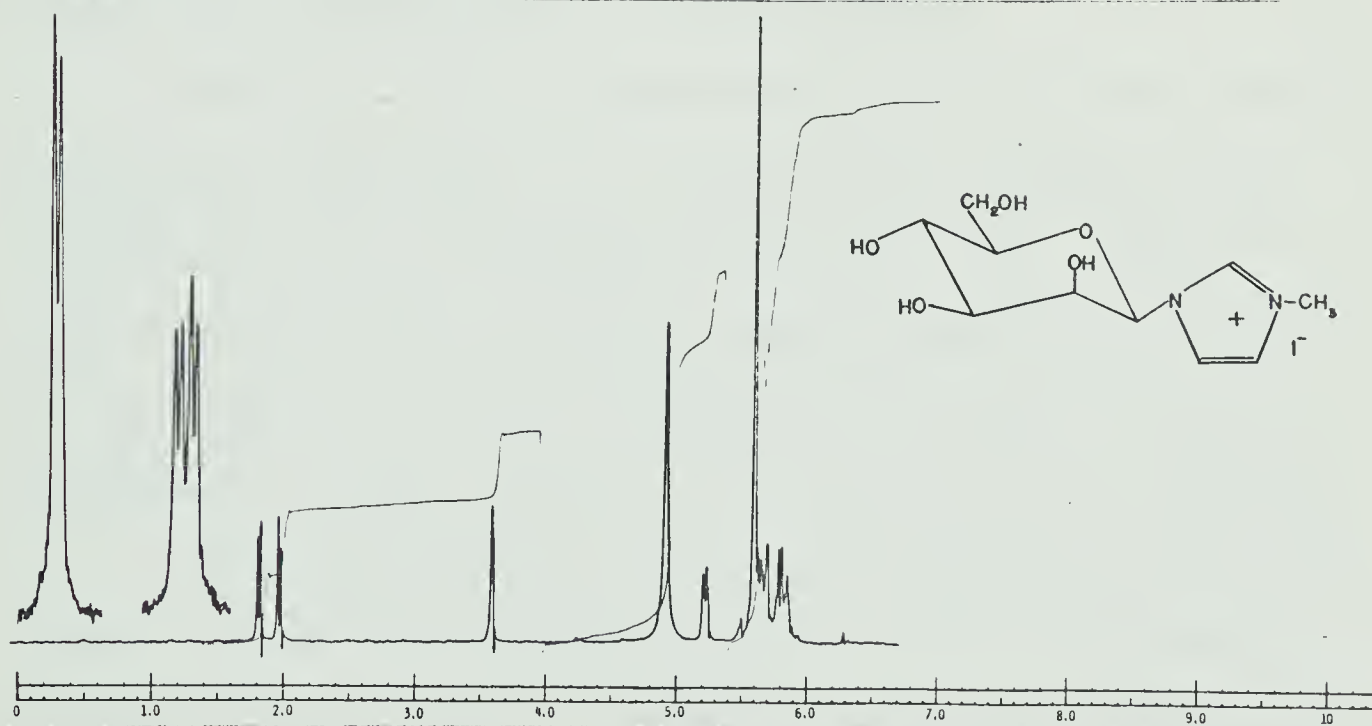


Fig. 24. N.m.r. spectrum (100 MHz) of 3-methyl-1-(β-D-mannopyranosyl)-imidazolium iodide (56) in deuterium oxide. Inset, sweep width 250 Hz.

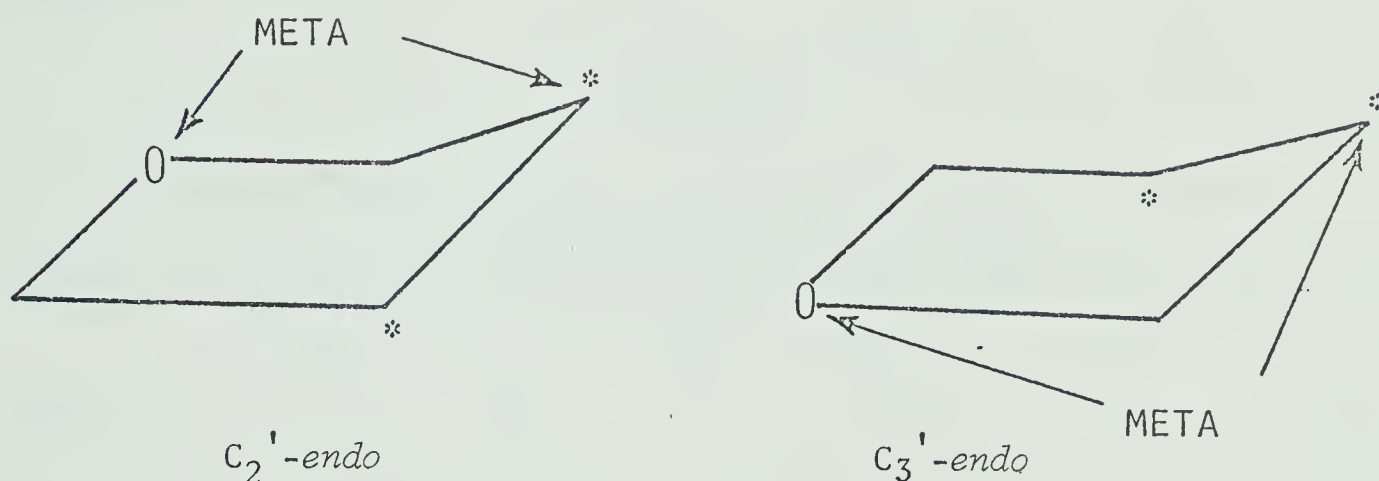
series (64). $J_{2',3'}$ observed was 2.7 Hz. On the other hand, 3-methyl-1-(β -D-mannopyranosyl)-imidazolium iodide gave $J_{1',2'} = 1.2$ Hz and $J_{2',3'} = 2.8$ Hz (Fig. 24). By comparing the n.m.r. parameters for 55 and its *N*-methiodide 56, one may conclude that these β -*N*-mannosides exhibit no conformational difference.

The quantitative line of argument employed in the discussion of the reverse anomeric effect in acetylated *N*-glucopyranosides and *N*-mannopyranosides may have been subject to some approximations. It still, however, represented a reasonable support to the proposed evaluation of the experimental results obtained on n.m.r. studies of the protonation and *N*-methylation of these glycosides. It is realized that similar treatment of at least the deacetylated *N*-mannopyranosyl-imidazoles would have been valuable. However this could not be achieved due to inadequate n.m.r. data available.

The shape of the nucleoside molecule (in the present work the ribofuranosyl imidazoles) is to a large extent determined by the conformation of the five-membered carbohydrate ring. Contrary to earlier beliefs (109), it has been shown by Sundaralingam (110) that the conformation of ribose is independent of whether the base is a pyrimidine or a purine molecule in both nucleosides and nucleotides.

The tetrahydrofuran ring, like the cyclopentane ring, is non planar (111) and thus energetically stable (112). The furanoside ring can in theory exist in a number of conformations depending on whether one (envelope conformation) or two (twist conformation) of the ring atoms are out of the plane formed by the remaining ring atoms. While investigating the configuration and conformation of

"di-D-fructose anhydride I," Lemieux and Nagarajan (113) concluded that "in general, furanoside rings will tend to be puckered in such a manner as to have a carbon meta to the ring oxygen (either the 2- or the 3-carbon for aldofuranosides) furthest out of the mean plane of the ring." This conclusion was well supported by the experimental evidence.



In cytidine the C_2' is out of the plane (114), in cytidine 3'-phosphate (115) and 5-bromo-5-deoxy thymidine (116) C_3' is out of the plane. Similar conclusion had been reached by several other workers (110, 117-119 and references cited therein). It is readily seen that when C_2' or C_3' atom is out of the plane of the ring, a greater number of bonds pass from the eclipsed to the *gauche* conformation than when the C_1 , C_4 or the oxygen atom are out of the plane of the ring. Accordingly, the conformations with the C_2' or C_3' atoms out of the plane of the ring are more stable. The displacement of these atoms out of the plane of the ring can occur either on the same or on the opposite side of C_5' , thus giving rise to *endo*- or *exo*- conformations,

respectively. It is interesting to note that the *endo*- conformation is most often encountered in nucleosides (118,119).

The conformational studies of *N*-D-hexopyranosyl imidazoles previously described and discussed are now extended to *N*-D-ribofuranosides. The 220 MHz n.m.r. spectrum of 1-(β -D-ribofuranosyl)-imidazole (57) is reproduced in Fig. 25 and the parameters are presented in Table 23.

TABLE 23

N.m.r. parameters (220 MHz in D₂O and 100 MHz in DMSO-*d*₆) of 1-(β -D-ribofuranosyl)-imidazole (57)

Solvent	H-1' (τ)	J _{1',2'} (Hz)	H-2' (τ)	J _{2',3'} (Hz)	H-3' (τ)	J _{3',4'} (Hz)
D ₂ O	4.94(d)	5.8	6.26(q)	5.2	6.40(q)	3.6
DMSO- <i>d</i> ₆	4.40(d)	5.2	-	-	-	-

On treatment with methyl iodide, 1-(β -D-ribofuranosyl)-imidazole (57) gave 3-methyl-1-(β -D-ribofuranosyl)-imidazolium iodide (58), the 220 MHz n.m.r. spectrum of which is reproduced in Fig. 26 and the parameters are presented in Table 24.

Using the original Karplus equation (68), Smith and Jardetzky (120) calculated the coupling constants for the sugar ring protons of D-ribose (in nucleosides and nucleotides) in all of the 20 possible conformations. Comparing these with the experimental results obtained in the present study and presented in Tables 23 and 24, it is apparent

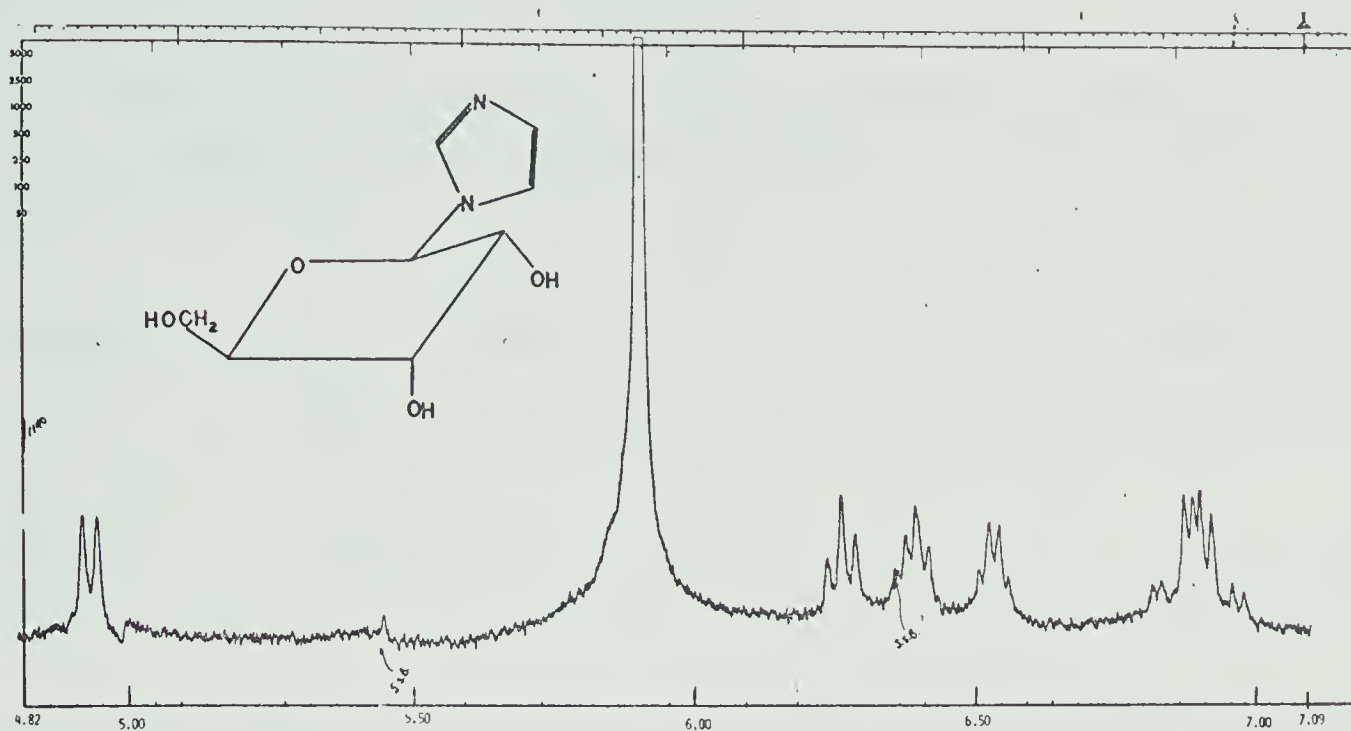


Fig. 25. N.m.r. spectrum (220 MHz) of 1-(β-D-ribofuranosyl)-imidazole (57) in deuterium oxide.

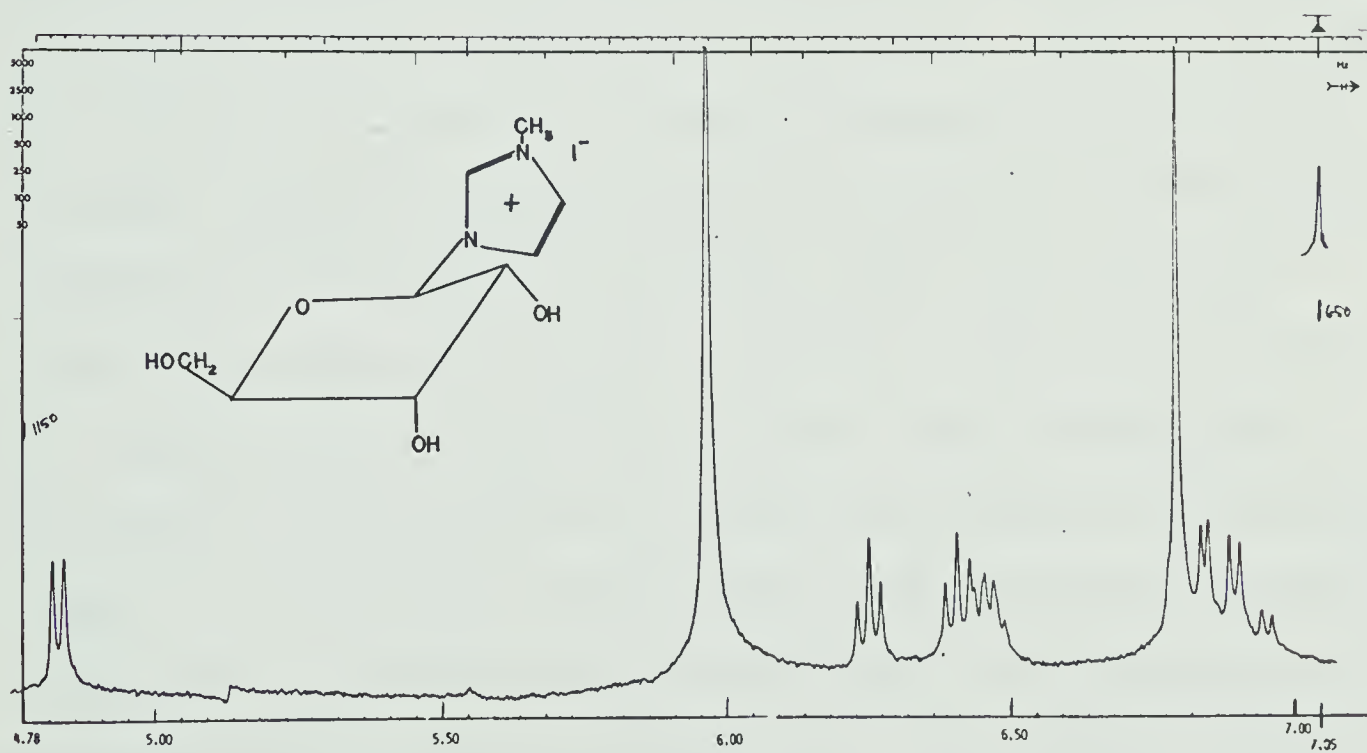


Fig. 26. N.m.r. spectrum (220 MHz) of 3-methyl-1-(β-D-ribofuranosyl)-imidazolium iodide (58) in deuterium oxide.

TABLE 24

N.m.r. parameters (220 MHz in D₂O and 100 MHz in DMSO-d₆) of
3-methyl-1-(β-D-ribofuranosyl)-imidazolium iodide (58)

	H-1'	J _{1',2'}	H-2'	J _{2',3'}	H-3'	J _{3',4'}	[⊕] N-CH ₃
Solvent	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)
D ₂ O	4.84(d)	4.2	6.25(q)	4.8	6.41(q)	4.9	-
DMSO-d ₆	4.27(d)	4.4	5.82(t)	~4.2	-	-	6.15

that both compounds 57 and 58 do not seem to exist solely in any of the possible conformations. As already stated (page 135) the C_{2'}-*endo* and C_{3'}-*endo* conformations of the ribofuranose ring are the most favorable ones, and the above mentioned results may best be interpreted in terms of C_{2'}-*endo* - C_{3'}-*endo* conformational equilibrium. Before considering and presenting a quantitative rationale to support this proposal, the knowledge of precise coupling constants for both C_{2'}-*endo* and C_{3'}-*endo* conformations is essential. The dihedral angles (ϕ) between the vicinal ring protons for both the conformations were required before the coupling constants could be calculated. These dihedral angles were deduced from consideration of X-ray data presented by Sundaralingam (110) about the projected valency angles of the ribofuranosyl moiety in CMP(C_{2'}-*endo*) and AMP(C_{3'}-*endo*), and assisted by the construction of the Drieding models of these two conformations. Thus obtained values of $\phi_{1',2'}$ and $\phi_{3',4'}$ for C_{2'}-*endo* conformation are 160° and 80°, respectively, and $\phi_{1',2'}$ and $\phi_{3',4'}$ for C_{3'}-*endo* conformations are 80° and 160°, respectively. These values were substituted into the

modified Karplus equation (72) which has already been discussed in the introduction (page 22). The following coupling constants were then obtained. $J_{1',2'} = 8.0$ and $J_{3',4'} = 0$ Hz for C_2' -endo; $J_{1',2'} = 0$ and $J_{3',4'} = 10.0$ Hz for C_3' -endo conformation. The only further assumption that has been made is that in C_2' -endo to C_3' -endo conformational change, the dihedral angle, and thus the vicinal coupling constant between H_2' and H_3' , remained the same.

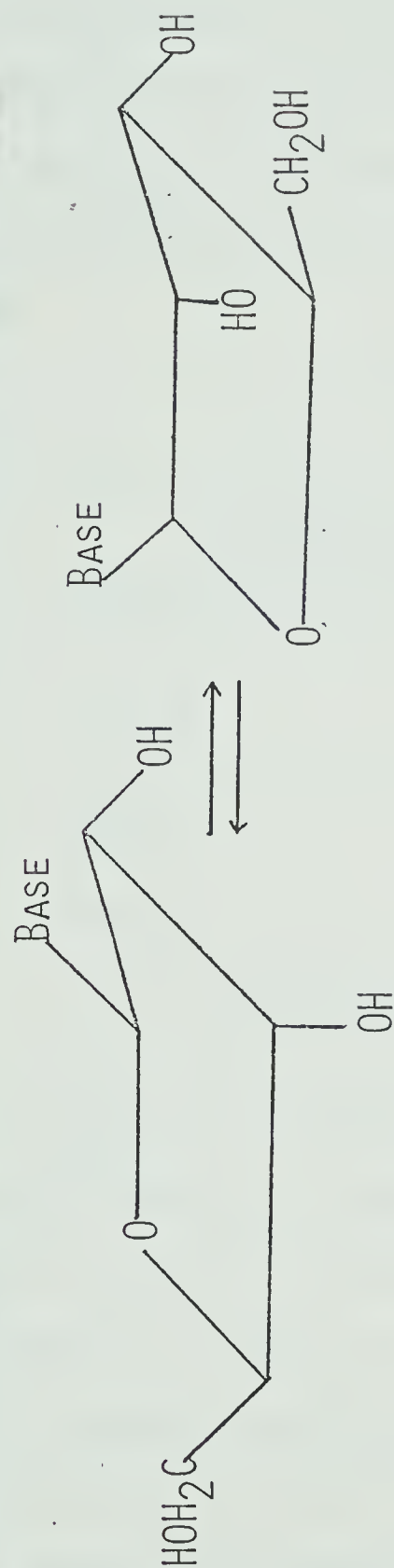
Considering the proposed C_2' -endo $\rightleftharpoons$ C_3' -endo equilibrium in the light of both the theoretically obtained coupling constants presented above, and the experimental values contained in Table 23 and 24, it is clear from Table 25 that:

(a) when the aglycon in 57 is imidazole, the equilibrium population of C_3' -endo conformation is 28% based on calculations using $J_{1',2'}$ and 34% based on $J_{3',4'}$.

(b) the quaternization of the imidazole ring shifts the position of the equilibrium towards the C_3' -endo conformation, its population now being 48% based on the calculations using $J_{1',2'}$ and 49% based on $J_{3',4'}$.

Taking into account the experimental errors involved, this represents a good agreement. Furthermore, the above assumption that there is no change in the dihedral angle and thus the vicinal coupling constant between H_2' and H_3' in going from C_2' -endo to C_3' -endo is also substantiated, since $J_{2',3'}$ is 4.8 and 5.2 Hz for 57 and 58, respectively, the 0.4 Hz difference being within the limits of experimental error. As may be concluded from the argument presented so far, the introduction of the positive charge on the nitrogen of

TABLE 25

Conformation equilibria for imidazole nucleosides 57 and 58 in D₂O

2'-endo

3'-endo

Calculated	J _{1',2'}	J _{3',4'} (Hz)	Q _{1',2'}	Q _{3',4'}
2'-endo	8.0	0	160°	80°
3'-endo	0	10.0	80°	160°
Experimental	% 3'-endo conformation			
Base	5.8		28	
		3.6	34	
			48	
H ₃ C-N ⁺	4.2	4.9	49	



the aglycon in the compound 57 to give 58 increases the population of the C_{3'}-*endo* conformation by about 20% which may be taken as a numerical manifestation of the reverse anomeric effect.

Similar observations were made in the case of acetylated analog, 1-(tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole (40), the n.m.r. spectrum of which is reproduced in Fig. 27 and the parameters are presented in Table 26.

TABLE 26

N.m.r. parameters (100 MHz) of 1-(tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole (40)

Solvent	H _{1'} (τ)	J _{1',2'} (Hz)
DMSO- <i>d</i> ₆	4.00 (d)	5.4
CDCl ₃	4.24	4.8 ^a

^aHalf width.

The n.m.r. spectrum of 3-methyl-1-(tri-*O*-acetyl-β-D-ribofuranosyl)-imidazolium iodide (59) is shown in Fig. 28 and the parameters presented in Table 27. It can readily be seen from Tables 26 and 27 that in DMSO-*d*₆ as solvent, the value of J_{J',2'} changed from 5.4 to 4.5 Hz on *N*-methylation of 40. This indicated the same type of preference for the C_{3'}-*endo* conformation by the nucleoside with the positive charge on the imidazole moiety (59), as was observed in the case of the deacetylated compound 58.

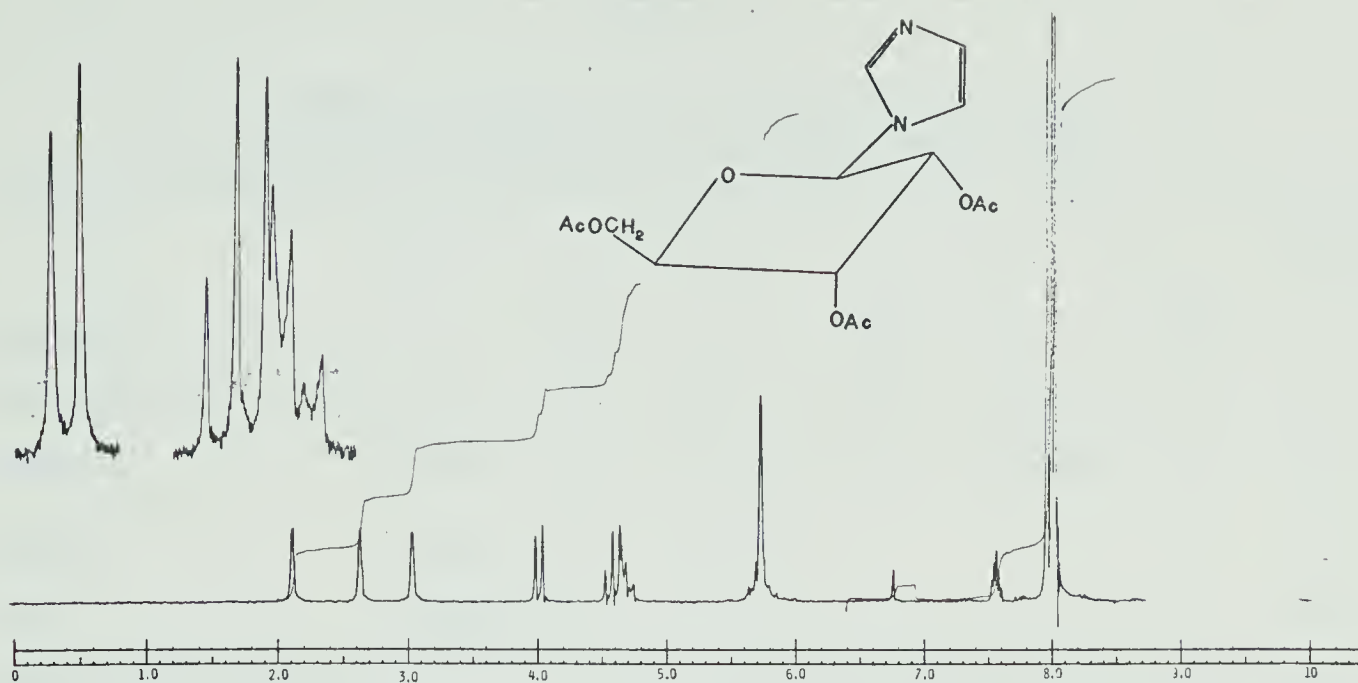


Fig. 27. N.m.r. spectrum (100 MHz) of 1-(tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole (40) in DMSO-*d*₆. Inset, sweep width 250 Hz.

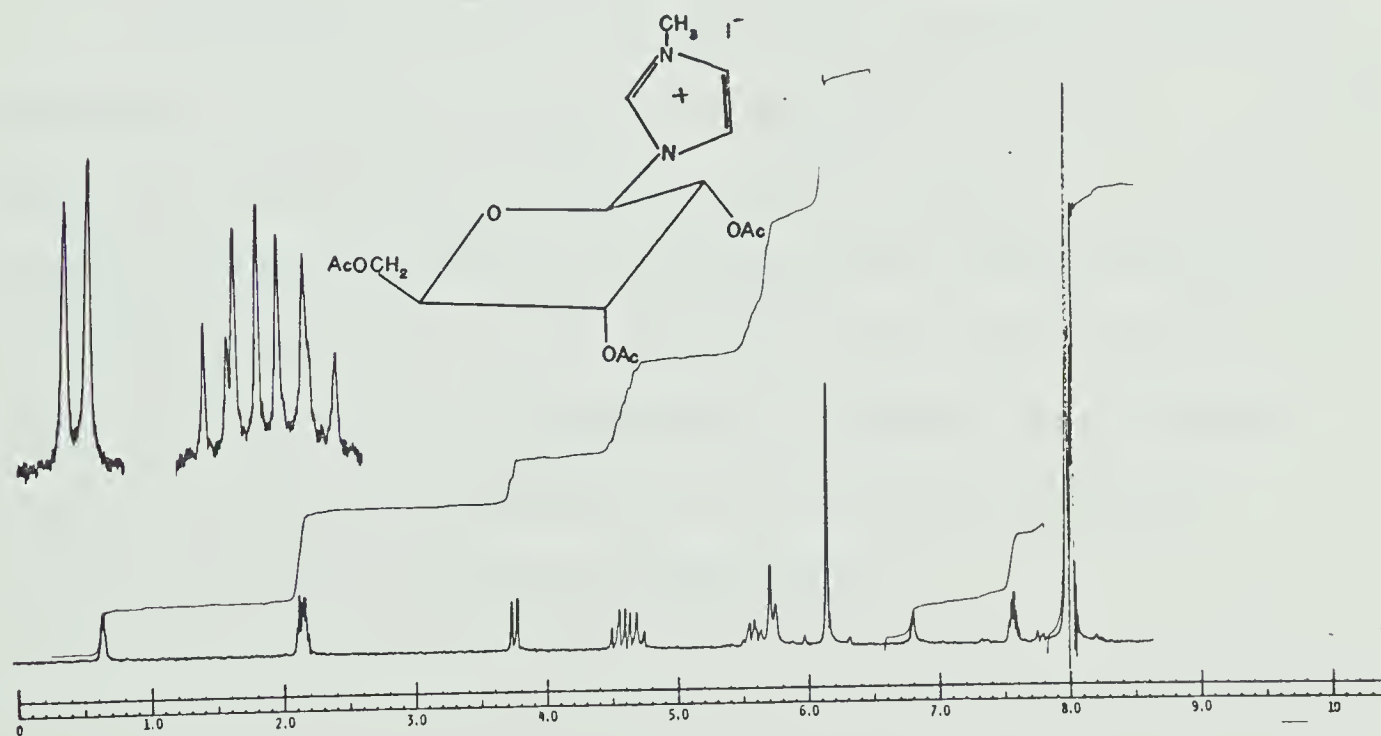


Fig. 28. N.m.r. spectrum (100 MHz) of 3-methyl-1-(tri-*O*-acetyl-β-D-ribofuranosyl)-imidazolium iodide (59) in DMSO-*d*₆. Inset, sweep width 250 Hz.

TABLE 27

N.m.r. parameters (100 MHz) of 3-methyl-1-(tri-*O*-acetyl-
 β -D-ribofuranosyl)-imidazolium iodide (59)

Solvent	H-1'	J _{1',2'}	H-2'	J _{2',3'}	H-3'	J _{3',4'}	$\text{N}^{\oplus}\text{-CH}_3$
	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)
DMSO- d_6	3.75(d)	4.5	4.57(q)	5.7	4.69(q)	5.1	6.14
CDCl ₃	3.70(d)	3.7	-	-	-	-	5.88
D ₂ O	3.28(d)	3.7	-	-	-	-	5.64

Further evidence for the reverse anomeric effect under discussion was sought by studying guanosine and its suitably *N*-methylated derivatives. The n.m.r. data obtained are summarized in Table 28.

On the basis of the above discussion, one would expect the pyrimidine nucleosides to show the reverse anomeric effect, as a partial positive charge could be developed on the nitrogen of the pyrimidine through conjugation with the C₂-carbonyl group, thus favoring the C_{3'}-*endo* conformation. On the other hand, purine nucleosides are not expected to show such a conformational preference. The literature survey for the n.m.r. parameters of the purine and pyrimidine nucleosides shown in Table 29 confirmed this.

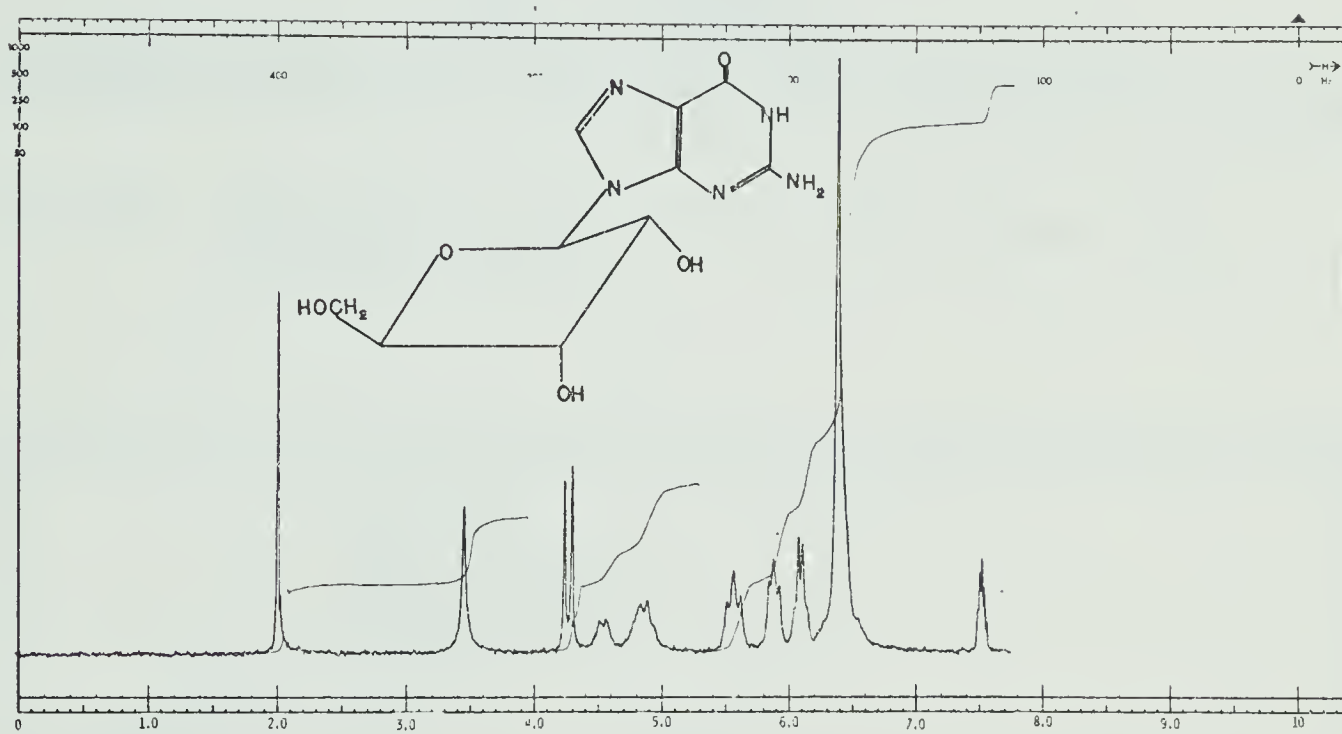


Fig. 29. N.m.r. spectrum (100 MHz) of guanosine (60) in DMSO- d_6 .

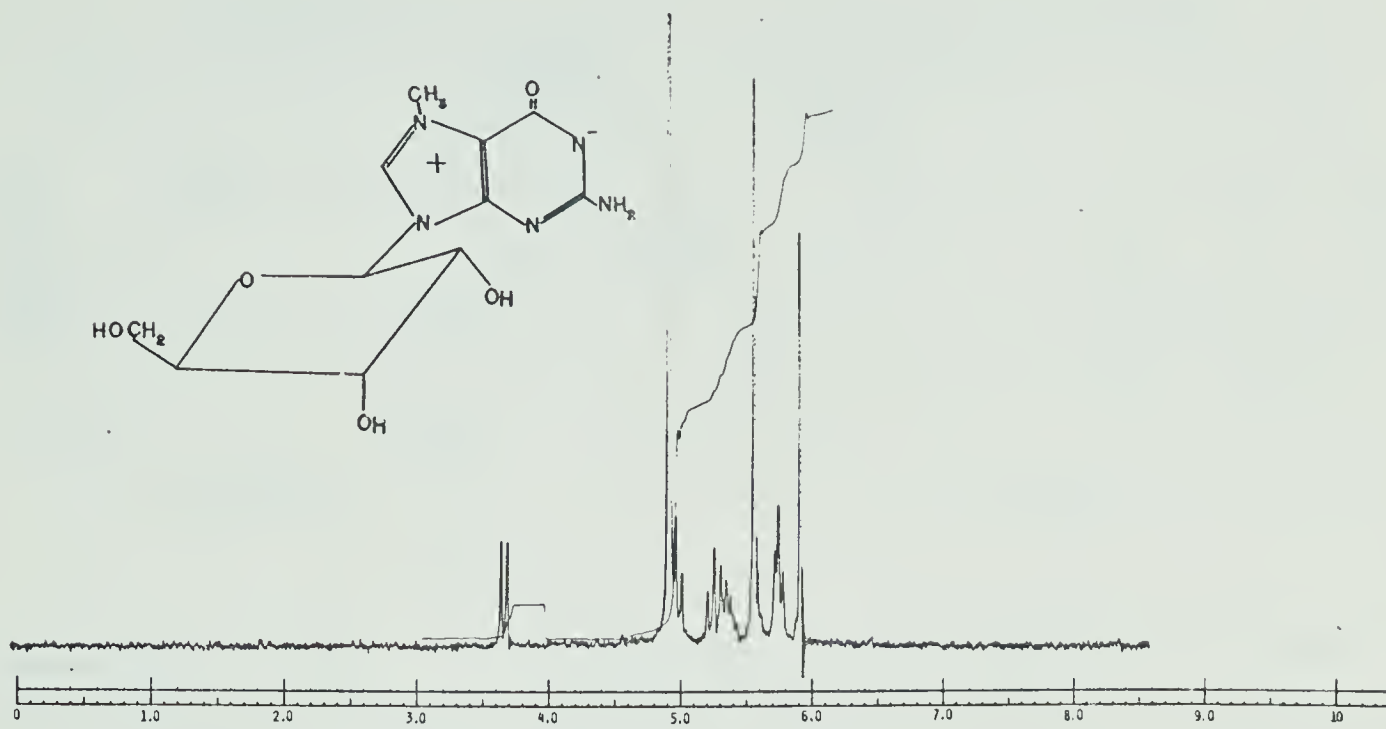


Fig. 30. N.m.r. spectrum (100 MHz) of 7-methyl guanosine (61) in deuterium oxide.

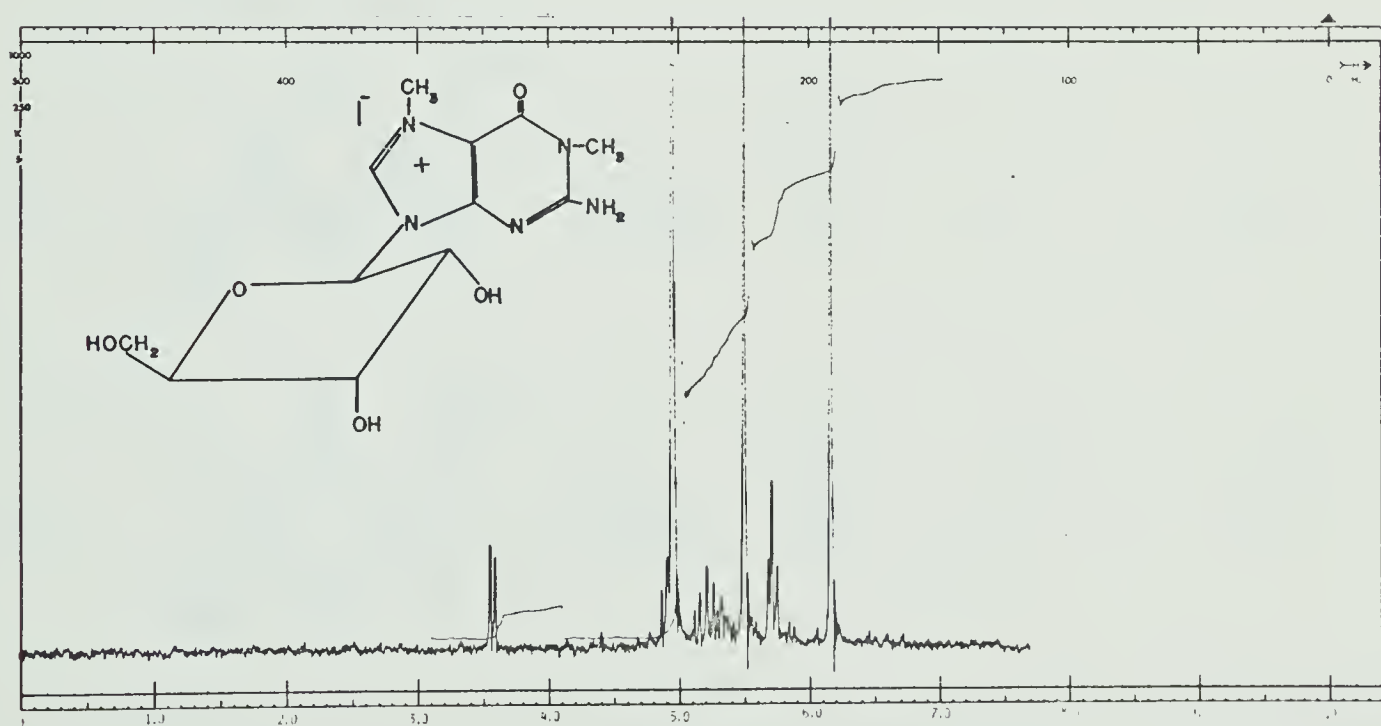
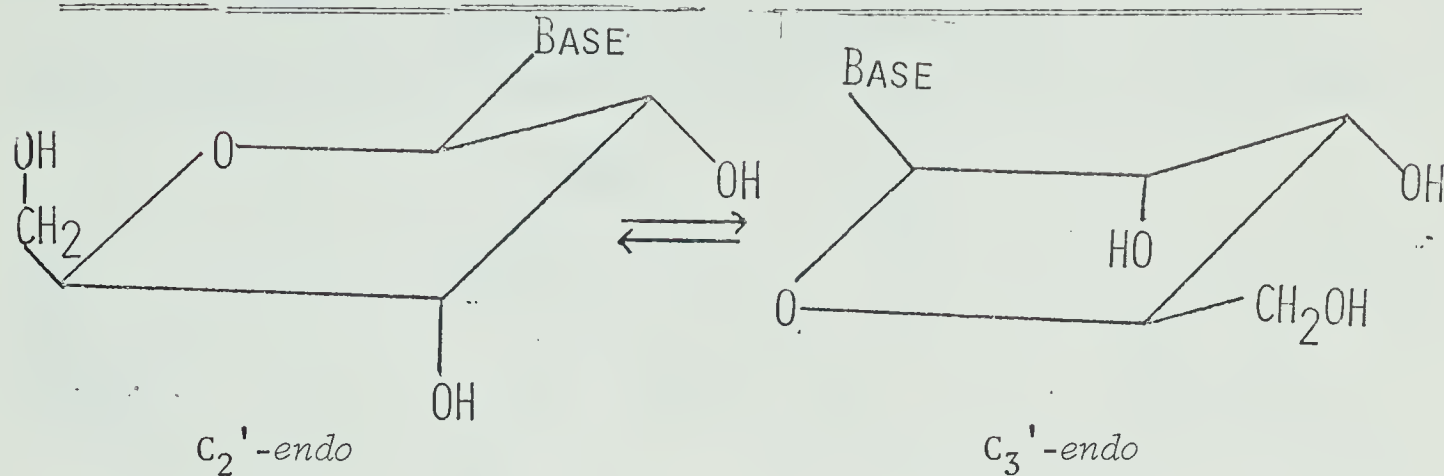


Fig. 31. N.m.r. spectrum (100 MHz) of 1,7-dimethyl guanosine iodide (62) in deuterium oxide.

TABLE 28

Conformational equilibria for guanosine nucleosides

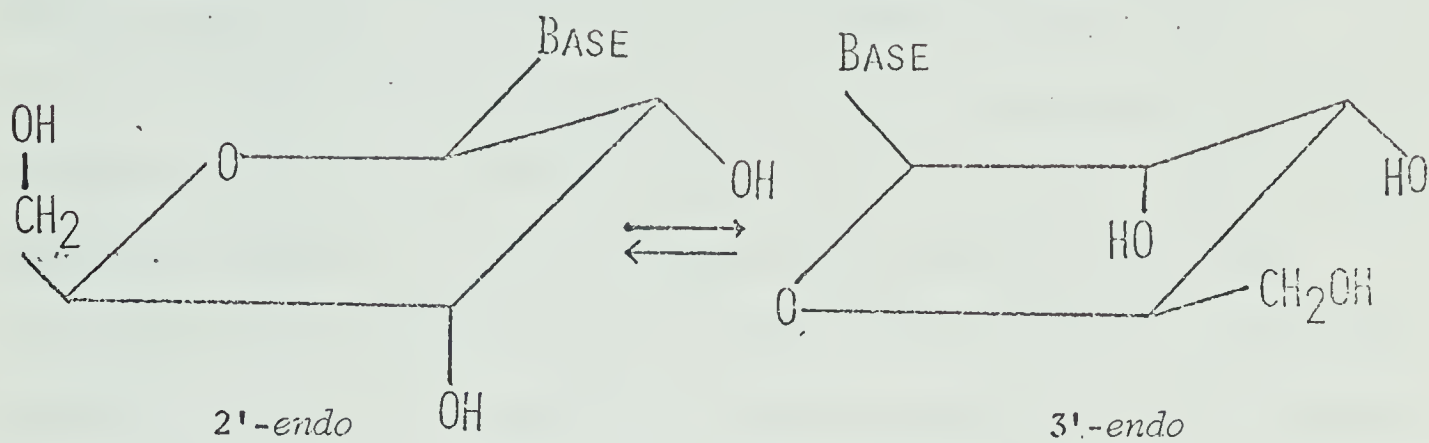


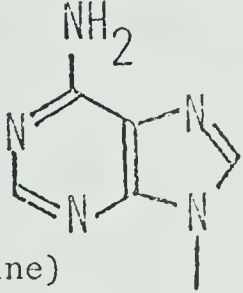
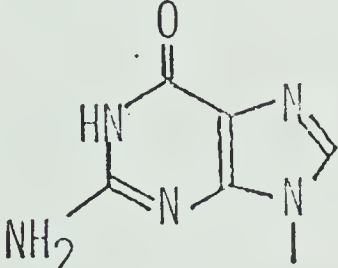
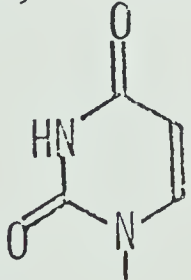
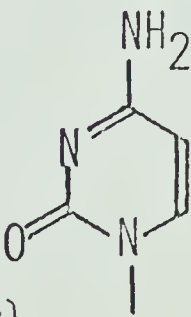
Compd. No.	Base	Solvent	$J_{1',2'}$ (Hz)	NMR Fig.	% 3'-endo
<u>60</u>		D_2O	6.4 ^a		20
		DMSO- d_6	5.9	31	26
<u>61</u>		D_2O	4.5	32	44
		DMSO- d_6	4.4		45
<u>62</u>		D_2O	3.5	33	56
		DMSO- d_6	4.1		49

^aRef. 144.60 Guanosine61 7-Methyl Guanosine62 1,7-Dimethyl Guanosinium Iodide

TABLE 29

Approximate conformational equilibria of purine and pyrimidine nucleosides in D₂O



Base	$J_{1',2'}$ (Hz)	% 3'-endo	Ref.
 (Adenosine)	5.7	29	121
 (Guanosine)	6.4	20	122
 (Uridine)	4.0	50	121
 (Cytidine)	3.0	62	123

Recently, Sarma and Kaplan (124) have reported the n.m.r. parameters for oxidized and reduced pyridine nucleotides. It can be seen from their results (Table 30) that when the oxidized coenzyme NAD^+ is converted to the reduced form NADH, the $J_{1',2'}$ (ribofuranosyl nicotinamide part of the molecule) increased from 5.1 to 8.1 Hz. On the other hand, the adenine $J_{1',2'}$ in the oxidized and reduced forms of the coenzyme remained approximately the same. Sarma and Kaplan (124) made similar observations in the cases of other nucleotides. These observations suggest that the conformation of the $\underline{\text{D}}$ -ribose attached to the adenine moiety of oxidized and reduced diphosphopyridine nucleotide is the same. The conformation of the $\underline{\text{D}}$ -ribofuranose attached to pyridine moiety of NAD^+ , however, by virtue of the reverse anomeric effect, seems to favor the C_3' -*endo* conformation. On the other hand the latter favors the C_2' -*endo* conformation as illustrated in Table 35.

In order to explain why the nucleosides and nucleotides with the aglycon carrying a positive charge show preference for C_3' -*endo* over C_2' -*endo* conformation, the following argument may be proposed. When models of imidazole nucleosides were examined, it was observed that in the case of C_3' -*endo* conformation, the imidazole ring carrying a positive charge seemed to eclipse with the free-electron lobe of the ring oxygen, thus stabilizing this conformation.

The n.m.r. spectrum of 1-(tri-*O*-acetyl- α - $\underline{\text{D}}$ -ribofuranosyl)-imidazole (39) is reproduced in Fig. 32 and the parameters presented in Table 31.

TABLE 30

Observed coupling constants (220 MHz) of the D-ribose moiety attached to the adenine and pyridine rings of NAD⁺ and NADH (124)

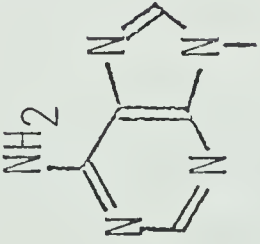
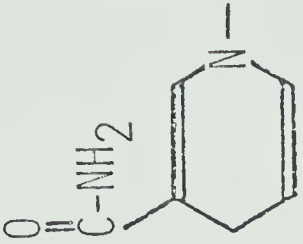
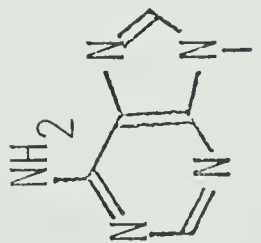
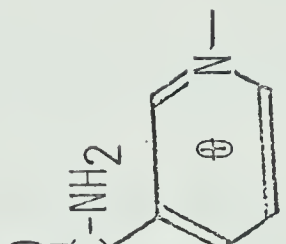
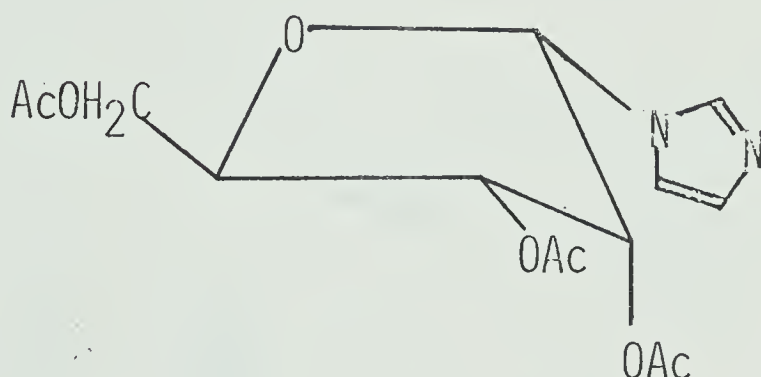
Nucleotide	Base	Adenine Ribose			Base	Pyridine Ribose	
		J _{1',2'}	J _{2',3'}	J _{3',4'} (Hz)		J _{1',2'} (Hz)	% 3'-endo
NADH		5.1	5.0	4.1		8.1	0
NAD ⁺		5.7	5.2	-		5.1	34

TABLE 31

N.m.r. parameters (100 MHz) of 1-(tri-*O*-acetyl- α -D-ribofuranosyl)-imidazole (39)

	H-1'	J _{1',2'}	H-2'	J _{2',3'}	H-3'	J _{3',4'}
	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)
DMSO- d_6	3.70(d)	5.2	4.50(t)	5.8	4.71(q)	4.9
CDCl ₃	3.88(d)	5.5	-	-	-	-

The values of the coupling constants observed for 39 suggest that the compound exists in the C_{2'}'-*exo* conformation as shown below:



In this conformation the three *cis*-substituents at C_{1'}, C_{2'} and C_{3'} are well staggered, thus avoiding any serious steric interactions. The n.m.r. spectrum of 3-methyl-1-(tri-*O*-acetyl- α -D-ribofuranosyl)-imidazolium iodide (63) is reproduced in Fig. 33 and the parameters presented in Table 32. The coupling constants J_{1',2'} and J_{2',3'} (in DMSO- d_6 for 39 and 63 (Table 31 and 32) remain approximately the same whereas J_{3',4'} changed from 4.9 in 39 to 3.3 Hz in 63. This variation in the coupling constant is not very serious and it may be

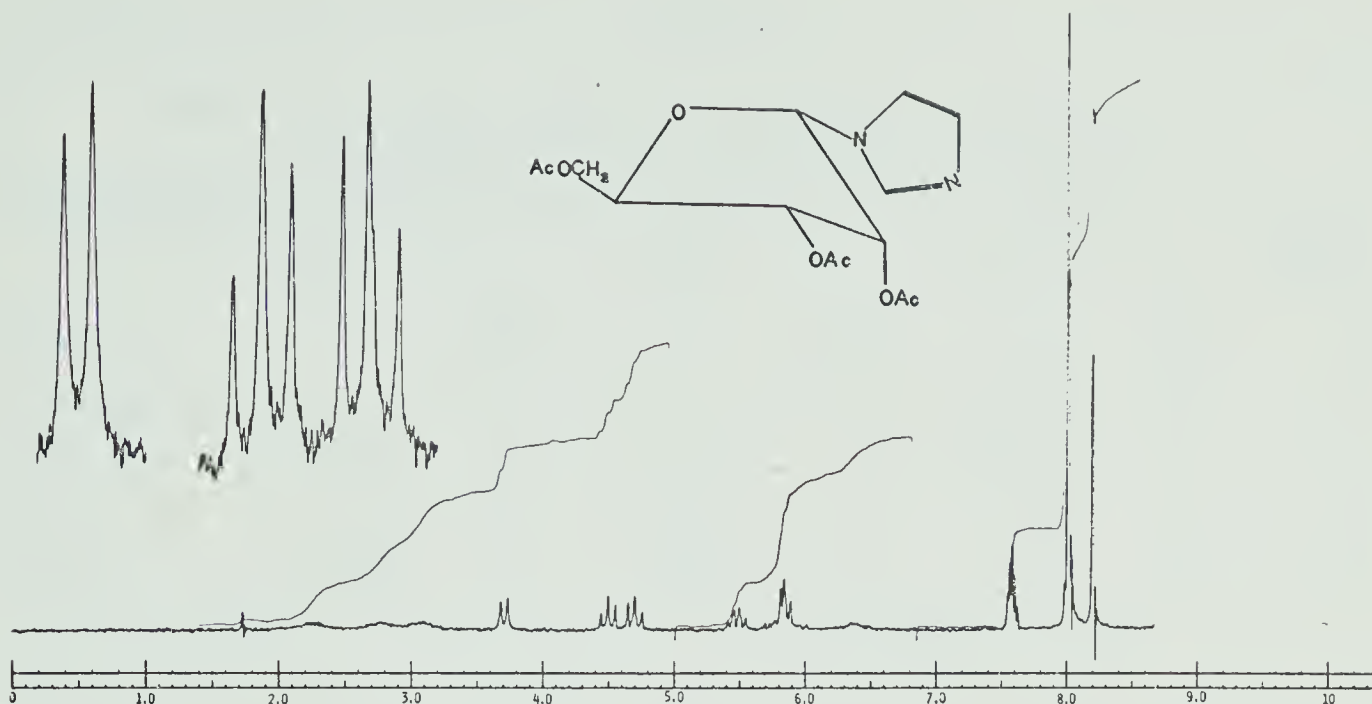


Fig. 32. N.m.r. spectrum (100 MHz) of 1-(tri-*O*-acetyl-α-D-ribofuranosyl)-imidazole (39) in DMSO-*d*₆. Inset, sweep width 250 Hz.

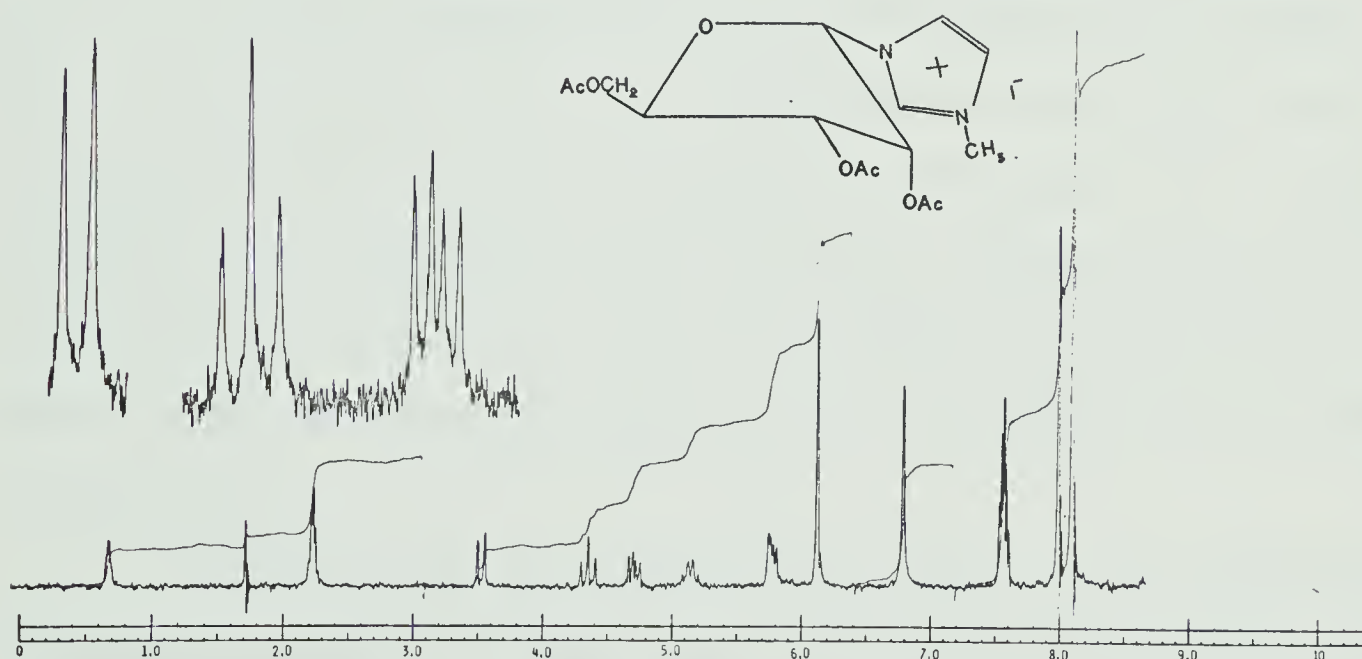


Fig. 33. N.m.r. spectrum (100 MHz) of 3-methyl-1-(tri-*O*-acetyl-α-D-ribofuranosyl)-imidazolium iodide (63) in DMSO-*d*₆. Inset, sweep width 250 Hz.

TABLE 32

N.m.r. parameters (100 MHz) of 3-methyl-1-(tri-*O*-acetyl- α -D-ribofuranosyl)-imidazolium iodide (63)

Solvent	H-1' (τ)	$J_{1',2'}$ (Hz)	H-2' (τ)	$J_{2',3'}$ (Hz)	H-3' (τ)	$J_{3',4'}$ (Hz)	$\text{N}^{\oplus}\text{-CH}_3$ (τ)
DMSO- d_6	3.53(d)	5.4	4.36(t)	5.4	4.71(q)	3.3	6.12
CDC1 ₃	3.23(d)	5.5	4.29(t)	5.5	4.48(q)	3.0	5.84

interpreted to imply that no significant conformational change takes place on *N*-methylation of the imidazole ring, i.e., going from 39 to 63.

The n.m.r. spectrum of the deacetylated 1-(α -D-ribofuranosyl)-imidazole (64) is reproduced in Fig. 34 and it exhibited a doublet for H_1' at τ 3.50 with a spacing of 4.3 Hz. On the other hand its methiodide, 3-methyl-1-(α -D-ribofuranosyl)-imidazolium iodide (65) showed a doublet for H_1' at τ 3.38 with a spacing of 4.8 Hz (Fig. 35). From the limited n.m.r. information available for these *O*-deacetylated- α -D-ribonucleosides 64 and 65 and in view of the conformations adopted by their fully acetylated analogs 39 and 63, C_2' -*exo* conformation may be assigned to 64 and 65.

From the results discussed in this section it may be concluded that the protonation or *N*-methylation of the imidazole ring of 1-(tetra-*O*-acetyl- α -D-glucopyranosyl)-imidazole (20), existing in 4C_1 conformation, causes a conformational change manifested as a conformational equilibrium between 4C_1 and 1C_4 conformations. 1-(tetra-*O*-acetyl- β -D-glucopyranosyl)-imidazole (21) as should be expected exhibits no

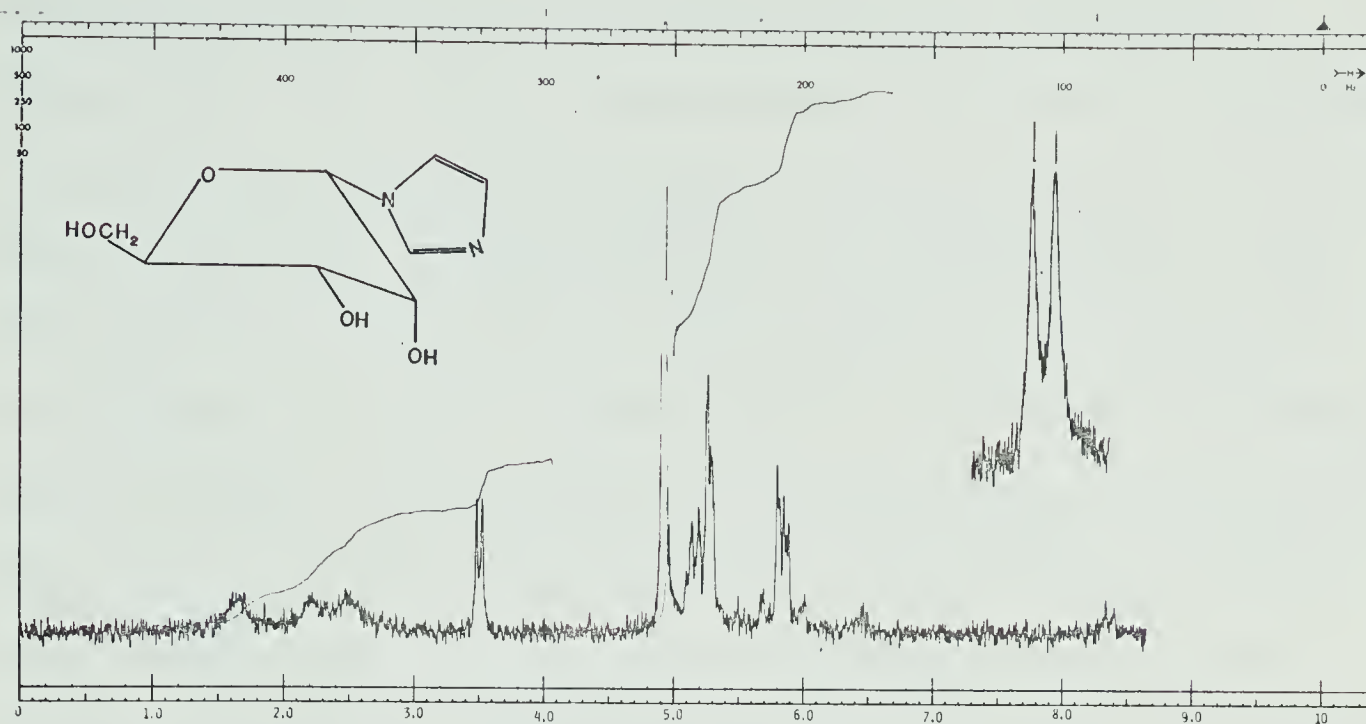


Fig. 34. N.m.r. spectrum (100 MHz) of 1-(α-D-ribofuranosyl)-imidazole (64) in deuterium oxide. Inset, sweep width 250 Hz.

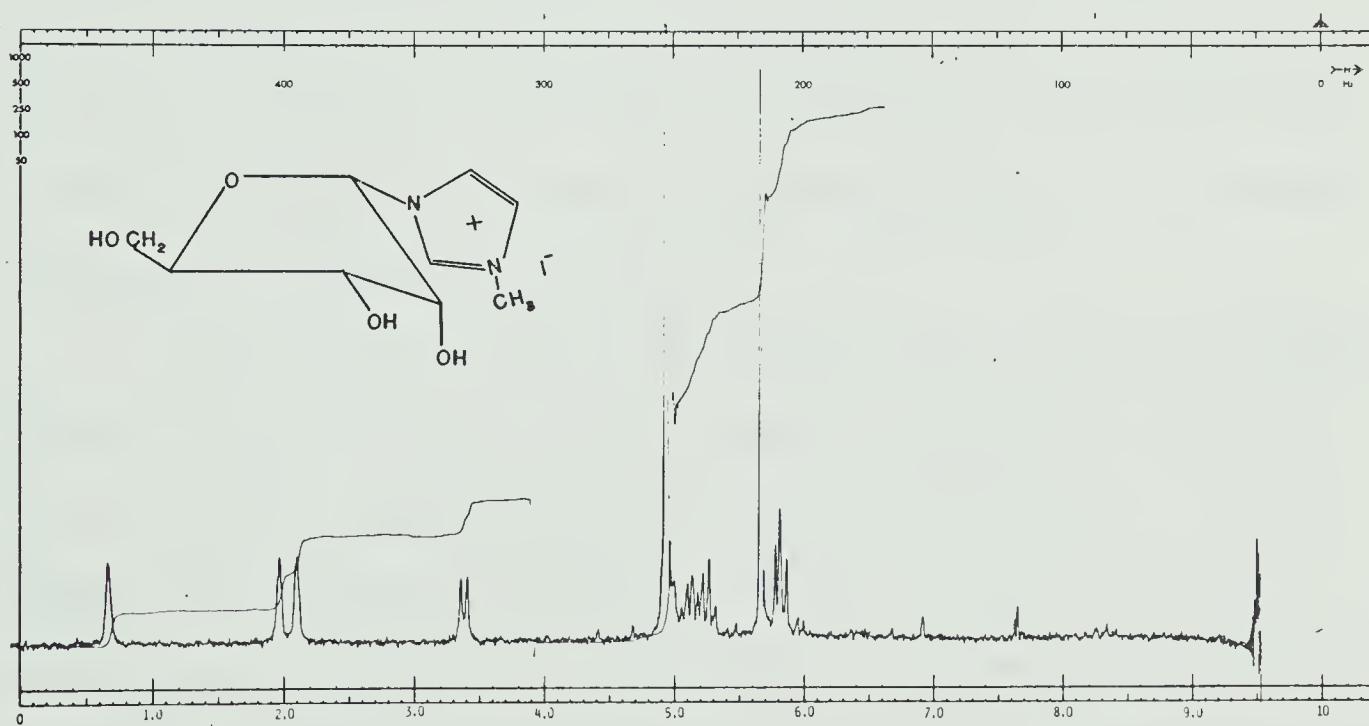


Fig. 35. N.m.r. spectrum (100 MHz) of 3-methyl-1-(α-D-ribofuranosyl)-imidazolium iodide (65) in deuterium oxide.

conformational change when the imidazole ring is *N*-protonated or *N*-methylated. It is not yet established why deacetylated α -*N*-glucosides do not show any conformational change on *N*-methylation of the imidazole ring. In this case an understanding of the intermolecular and intramolecular interactions that come into operation once the protecting acetyl groups are removed is undoubtedly necessary before any explanation could be offered. The examination of α -*N*-mannosides (both acetylated and deacetylated) show that although they already exist in a conformational equilibrium, ${}^4C_1 \rightleftharpoons {}^1C_4$, there is a definite increase in the contribution by 1C_4 conformation on protonation or *N*-methylation of the imidazole ring. As may be predicted β -*N*-mannopyranosides (deacetylated and acetylated) show no conformational changes. The reason for the evident difference in behavior of deacetylated α -*N*-glucopyranosides and mannopyranosides may now further be attributed to mostly the intramolecular interactions. The above conclusions are supported by the similar observations of Onodera and coworkers (66,67) in the behavior of glucose and mannose α -*N*-purines.

In the case of *N*-ribofuranosyl imidazoles, the reverse anomeric effect is found to operate in the β -anomers, whereas the α -anomers exist in C_2' -*exo* conformation only. Because of the reverse anomeric effect β -*N*-ribofuranosyl imidazoles exhibit a C_2' -*endo* - C_3' -*endo* conformational equilibrium; *N*-methylation of the imidazole moiety causing an increase in the contribution of C_3' -*endo* conformation to the equilibrium. Similar observations were made in the cases of purine and pyrimidine ribonucleosides and nucleotides.

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